Draft Comparative Effectiveness Review

Number XX

Systematic Review of Calcineurin Inhibitors for Renal Transplant

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AHRQ Publication No. xx-EHCxxx
<Month Year>

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: <Authors>. Systematic Review of Calcineurin Inhibitors for Renal Transplant. Comparative Effectiveness Review No. ##. (Prepared by the <EPC Name> Evidence-based Practice Center under Contract No. <##>.) AHRQ Publication No. XX-EHCXXX-EF. Rockville, MD: Agency for Healthcare Research and Quality. <Month Year>. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Systematic Review of Calcineurin Inhibitors for Kidney Transplant

Structured Abstract

Background: The calcineurin inhibitors (CNIs), cyclosporine and tacrolimus are the cornerstone of immunosuppression for renal transplantation. CNIs are effective but must be managed carefully to avoid toxicity. Routine CNI monitoring is used to guide dosing, but uncertainty surrounds the optimal method and timepoint for monitoring patients. Additionally, strategies to reduce CNI exposure through use of lower therapeutic levels, or replacement with other immunosuppressants, have been adopted, but the comparative effectiveness of these approaches is not clear. This systematic review evaluates the evidence for three Key Questions. The first question compares immunoassay analysis with liquid chromatographic or mass spectrometric analytical techniques for therapeutic monitoring of CNIs. The second question examines optimal drug monitoring timepoints for patients receiving cyclosporine A therapy. The third question evaluates alternative strategies to full-dose CNI regimens.

Methods: Literature searches were performed in EMBASE, MEDLINE, PubMed, the Cochrane Library, and gray literature sources. Searches covered the literature published from 1994 through July 2014. Studies were eligible for inclusion if they were English-language studies of adult renal transplant recipients. Studies of patients at low, average, and high risk of rejection, including all donor types and retransplants, were eligible. Multi-organ recipients were excluded. Data were extracted, synthesized, and meta-analyzed when appropriate. We assessed studies for risk of bias and evaluated the strength of evidence for important outcomes.

Results: Ninety-seven studies were included. Seven studies addressed Key Question 1, six studies addressed Key Question 2, and 84 studies addressed Key Question 3. Eighty-seven studies were randomized controlled trials, and 10 were non-randomized controlled studies.

For the first Key Question, which evaluated monitoring strategies, one small study compared clinical utility outcomes associated with using chromatographic techniques versus immunoassays, and demonstrated insufficient evidence to determine if outcomes differed by technique. Seven studies assessed analytical performance measures. Findings suggested chromatographic techniques are more accurate and precise than commonly used immunoassays, but the clinical relevance of these differences is unclear.

The second Key Question included six studies that compared monitoring of cyclosporine A (CsA) at trough versus 2-hour timepoints and provided low strength evidence suggesting no difference in risk of acute rejection between the monitoring timepoints. The evidence comparing monitoring timepoints was largely inconclusive for other clinical outcomes.

Eighty-four studies examined alternative regimens that limited or avoided exposure to CNI therapy. Thirty-six studies of low-dose CNI treatment provided high strength evidence that minimization was associated with improved clinical outcomes, including improved renal function and reduced risk of acute rejection and graft loss. Early timing was better than later

minimization, while the role of induction therapy was not clear. Twenty-one studies examined outcomes associated with conversion of patients from a CNI to alternative immunosuppressive therapies, usually mTOR inhibitors. High-strength evidence indicates that patients converted from a CNI may experience increased risk of acute rejection. Moderate-strength evidence suggests that conversion may result in improved renal function. Fifteen studies examined withdrawal of CNI therapy. These studies found high-strength evidence suggesting that withdrawal was associated with increased risk of acute rejection and graft loss. Finally, eight studies evaluated regimens that avoided CNIs and instead used sirolimus or belatacept from the immediate post-transplant period. These studies were heterogeneous and could not be combined for meta-analysis, but moderate-strength evidence suggests renal function was better in patients not receiving CNI treatment. Evidence for other outcomes was low-strength or insufficient to support conclusions.

Conclusions: The findings of the studies addressing monitoring techniques provide insufficient evidence to determine if clinical outcomes differ by technique. Although studies comparing the analytical validity of the different approaches suggest that chromatographic technologies may be more accurate and precise in their measurement of CNI concentration when compared with commonly used immunoassays, it is unclear whether this increase in measurement accuracy and precision is associated with improved clinical outcomes. Further research is necessary that directly compares monitoring techniques and assesses clinical validity or utility measures.

For the Key Question assessing monitoring timepoints, current evidence is insufficient to suggest whether one approach is better than the other. More studies directly comparing the benefits and harms of two hour monitoring with trough monitoring are needed.

For the third Key Question, studies suggest that immunosuppression with low-dose cyclosporine or tacrolimus results in improved renal function and reduced risk of harm. These benefits may be most significant when initiated from the time of transplant or shortly thereafter. Use of induction agents is not strongly associated with improved outcomes in minimization regimens, but additional research is necessary to clarify the effect of induction therapy. Strategies that employ conversion from a CNI to an mTOR inhibitor are associated with improved renal function but higher incidence of acute rejection. Regimens that withdraw CNI were not associated with improved renal function and may increase the risk of acute rejection. Avoidance strategies employing de novo use of immunosuppressive drugs other than CNIs have not been studied widely, and further research is necessary to identify potential benefits or harms of complete CNI avoidance.

Alternative regimens have been studied primarily in low-risk populations, and further research is necessary to identify successful immunosuppression strategies for high-risk patients. More comprehensive and consistent reporting of important outcomes is also needed, including measures of renal function, CNI-related toxicity, and patient adherence to immunosuppressive regimens.

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Introduction

Background

Approximately 17,000 renal transplants occur each year in the United States, accounting for almost 60% of all organ transplants.[1] Kidney transplantation is the treatment of choice for end-stage renal disease. Causes of renal failure are varied, including diabetes, hypertension, glomerular and cystic kidney diseases, and autoimmune disorders. Kidney transplantation offers a better quality of life and a survival benefit over chronic dialysis for most patients. The 2013 Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients annual report showed that the conditional graft half-life (defined as the time to when half the grafts surviving at least 1 year are still functioning) was 11.9 years for deceased donor transplants and 15.9 years for living donor transplants in 2011.[2] Survival rates continue to improve; a recent analysis of more than 250,000 renal transplant recipients demonstrated that death-censored graft half-life for all deceased donor transplants increased from 10.2 years in 1989 to 14.3 years in 2005 and remained approximately 16.5 years for living donor transplants during the same time period.[3]

Calcineurin inhibitors (CNIs) are the cornerstone of immunosuppression for renal transplantation. Cyclosporine A (CsA) and tacrolimus (TAC) are the two agents composing this drug class and have been used in renal transplant recipients for over 20 years. CsA was initially approved in 1983 by the U.S. Food and Drug Administration (FDA) for immunosuppression following organ transplantation; in 1995, a microemulsion formulation of CsA (associated with better bioavailability and more consistent absorption) was approved. CsA formulations are usually administered twice daily. TAC received FDA approval in 1994 for liver transplant recipients and in 1997 for renal transplant recipients. Tacrolimus is usually administered twice daily but recently became available as an extended-release once-daily formulation. FDA-approved generic equivalents are available for TAC immediate-release formulations, as well as modified and unmodified CsA.

TAC-based regimens are currently the mainstay at most renal transplant programs in the United States. More than 85% of renal transplant recipients are discharged from admission on TAC as part of their maintenance immunosuppressive regimen.[2] This is largely because TAC is more potent and associated with less rejection and nephrotoxicity than CsA.[4] However, TAC is also associated with more neurotoxicity and gastrointestinal side effects than CsA.[5] It has also been associated with an increased incidence of new-onset diabetes and the development of metabolic syndrome, which are significant concerns because the main cause of death among renal transplant recipients is cardiovascular disease.[6,7]

CNIs are effective immunosuppressants, but they have extensive toxicity profiles. TAC and CsA both require careful management to ensure sufficient dosing for therapeutic effectiveness while avoiding toxicity. Two primary strategies have been employed to balance efficacy while limiting side effects: routine monitoring of CNI drug levels to guide dosing adjustments and minimization of CNI use to the lowest therapeutic levels. Alternatively, CNI use may be withdrawn or avoided entirely in favor of other immunosuppressant therapies.

CNI Monitoring

The primary assays used for monitoring CNI drug levels are mass spectrometry and immunoassays. CsA is measured with high-performance liquid chromatography (HPLC),

fluorescence polarization immunoassay (FPIA), enzyme-multiplied-immunoassay techniques (EMIT), or liquid chromatography-tandem mass spectrometry (LC-MS/MS). TAC can be monitored with LC-MS/MS, enzyme-linked immunosorbent assay (ELISA), or microparticle enzyme immunoassay (MEIA). Compared with the immunoassays, HPLC and LC-MS/MS offer more precise measures of the parent compound while minimizing measurement of metabolites, but they can also be more expensive, time-consuming, labor-intensive, and less standardized techniques, making their performance provider-dependent. It is also unclear whether long-term health outcomes vary with each assay methodology.

The ability to accurately measure low-range CNI concentrations is important because CNI target therapeutic ranges have decreased over time.[8] The Report of the European Consensus Conference recommends that assays achieve a limit of quantification of 1 ng/mL.[8] However, randomized trials demonstrating the value of CNI monitoring itself are lacking. Moreover, although LC-MS/MS is one of the most popular methods for currently measuring TAC, no standardization exists between laboratories.

Selection of the appropriate timing for measuring CNI drug levels is another important component of clinical care. It is recommended that TAC be monitored at trough levels (usually just before morning dose administration) as this timepoint is thought to correlate well with the total exposure to the drug over the past 12 hours. However, a recent publication reported that pooled data from three large randomized controlled trials (RCTs) was unable to find any significant correlations between TAC trough levels at 5 time points (day 3, 10, and 14, and months 1 and 6 post-transplant) and the incidence of biopsy proven acute rejection in renal transplant recipients.[9]

Trough monitoring of CsA (C0) is also common, but recent research has suggested that monitoring CsA at 2 hours after dosing (C2) yields effective monitoring while enabling lower doses and less risk of toxicity.[10,11] However, C2 level monitoring is less practical because it needs to be measured within 15 minutes of the two hour target in order to avoid large shifts in concentrations, while C0 measurement can be done within a 10- to 14-hour window. The question of whether C0 monitoring should be replaced with monitoring at C2 is unresolved, and determining the optimal timepoint can lead to more efficient, safer, and higher value care.

CNI Management and Minimization Strategies

Immunosuppressive regimens designed to reduce or eliminate exposure to CNI toxicity risks have been investigated in recent years.[12] Four alternative approaches (see Table 1) to full-dose CNI therapy have emerged: 1) CNI minimization, which reduces the amount of the drug administered. This strategy may be undertaken from the time of transplant (de novo), or later post-transplant (elective) as a result of an adverse event such as nephrotoxicity or BK viral infection; 2) CNI conversion, which tapers CNI dosing at any time post-transplant until full replacement with alternative immunosuppressants is achieved. This strategy may be undertaken at any time post-transplant and is usually a result of an unacceptable CNI-related adverse event; 3) CNI withdrawal, which slowly eliminates the amount of drug administered early or late post-transplant; 4) CNI avoidance, which avoids the use of CNI in favor of other immunosuppressive drugs from the outset. These strategies also involve the use of concurrent immunosuppressants in standard or low doses and may also include induction agents to provide added immunosuppression in the immediate post-transplant period. The other immunosuppressive drugs often used include mycophenolic acid formulations such as mycophenolate mofetil (MMF) or enteric-coated mycophenolic sodium (EC-MPS), mammalian target of rapamycin (mTOR)

inhibitors such as sirolimus (SRL) or everolimus (EVR), azathioprine (AZA), and belatacept. No clear consensus exists regarding the comparative efficacy and safety of these alternatives to full-dose CNI regimens.

Table 1. Alternatives to full-dose CNI regimens

Strategy	Definition	Timing
Minimization	Lower dosage of CNI	Planned de novo, or result of adverse event
Conversion	Tapering of CNI dose until eliminated and replaced with other immunosuppressant	Usually result of adverse event
Withdrawal	Tapering of CNI dose until eliminated; continuation of other immunosuppressant already in use before withdrawal	Planned de novo or result of adverse event
Avoidance	No CNI given; other immunosuppressant used	Planned de novo

CNI = calcineurin inhibitor

Another important consideration is treating high-risk populations. Advances in immunosuppression and improved transplant outcomes have led to liberalized criteria for organ donors and recipients (e.g., human immunodeficiency virus (HIV) is no longer a universal contraindication to transplantation). These patients present special challenges because there are drug-drug interactions between CNIs and protease inhibitors.[13,14] Additionally, as the volume of patients seeking retransplantation grows, the number of highly sensitized patients has increased, as has the popularity of desensitization protocols employing high-dose induction and maintenance immunosuppression.[15] As more potent TAC-based immunosuppression has become the clinical standard, opportunistic infections such as cytomegalovirus (CMV), Epstein Barr virus (EBV), and BK viremia and nephropathy have emerged as complications, and data suggest these are more common with TAC than with CsA.[16,17] Immunosuppressive regimens that minimize or avoid CNIs may play an important role in the care of such patients.

Scope and Key Questions

The main objective of this report is to conduct a systematic review and meta-analysis of the benefits and harms of CNIs as maintenance therapy for adults who have undergone a renal transplant. In this review, we address the following Key Questions (KQs):

Monitoring Assays for Calcineurin Inhibitors

Key Question 1a. In adult renal transplants, how do liquid chromatographic and mass spectrometric analytical techniques compare with immunoassay analysis for therapeutic monitoring of full dosing regimens of the calcineurin inhibitors (CNIs) cyclosporine and tacrolimus?

Key Question1b. In adult renal transplants, how do liquid chromatographic and mass spectrometric analytical techniques compare with immunoassay analysis for therapeutic monitoring of lower CNI doses used in minimization, conversion, or withdrawal strategies?

Cyclosporine Monitoring Timepoints

Key Question 2. In adult renal transplants, how does two-hour post-administration cyclosporine monitoring (C2) compare with trough monitoring (C0) for health outcomes?

Management of Alternatives to Full Dose CNI Regimens

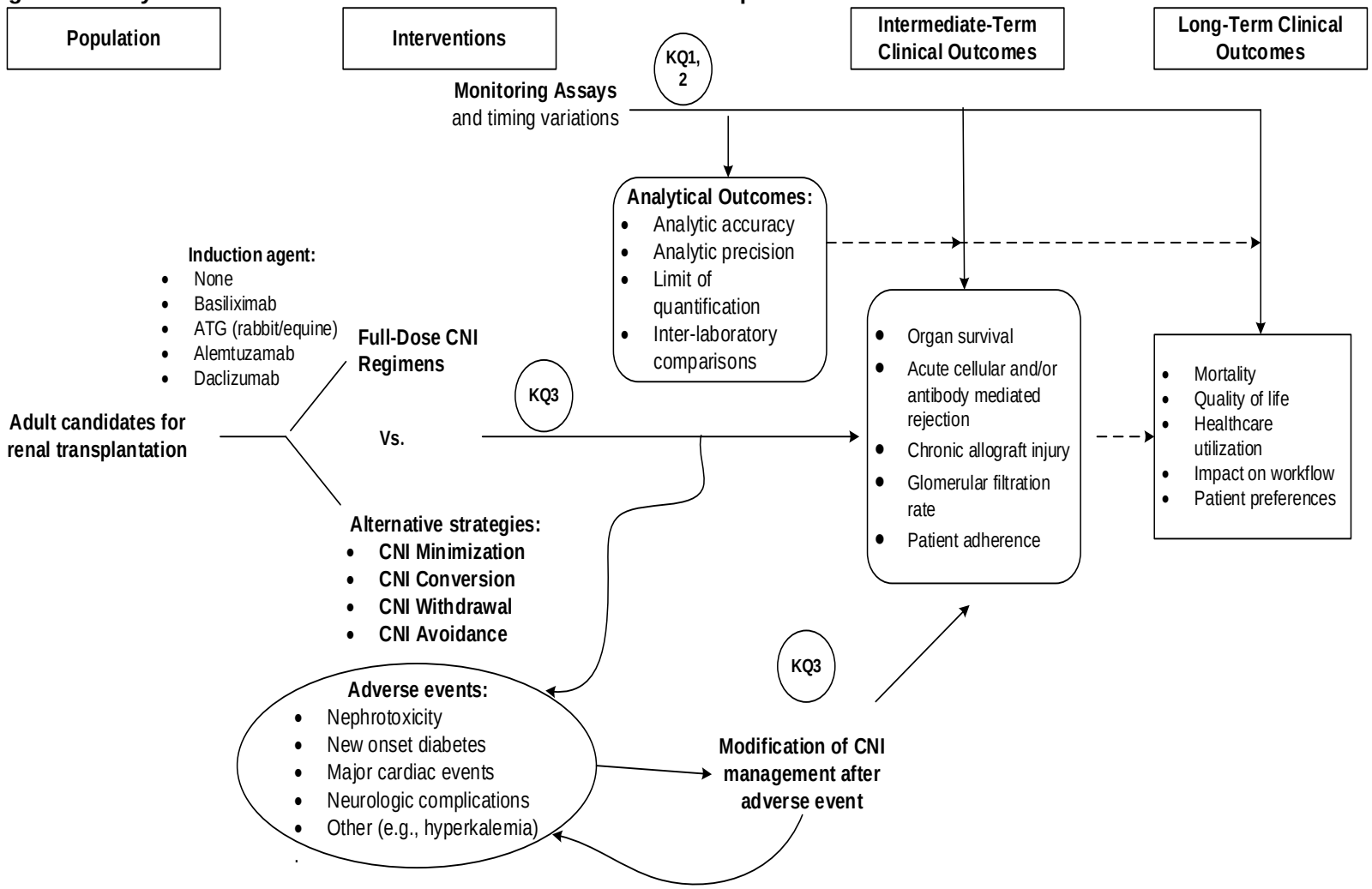
Key Question 3a. In adult renal transplants, how do immunosuppressive regimens designed to reduce or eliminate exposure to CNI toxicity compare with each other and with full dose CNI regimens for health outcomes?

Key Question 3b. How does the type of induction agent (including when no induction is used,) and the use of concurrent immunosuppressive agents, impact outcomes of regimens that reduce or eliminate CNI exposure?

Analytic Framework

We developed an analytic framework to guide the systematic review process (Figure 1).

Figure 1. Analytic framework for Calcineurin inhibitors for renal transplant



Organization of This Report

In the remaining three chapters of this report, we discuss the methods for this systematic review, the results for each key question, and the findings. Within the Results chapter, we provide the results of the literature searches and screening procedures, as well as descriptions of included studies, key points, detailed syntheses of the studies, and strength-of-evidence tables for each KQ. The Discussion chapter reviews the key findings and strength of evidence for each KQ, places the findings in the context of previous systematic reviews, examines the general applicability of the studies, discusses implications for decisionmaking, describes limitations of the systematic review process and the evidence base for each KQ, and identifies knowledge gaps that require further research.

A list of acronyms and abbreviations appears after the references, followed by five appendixes. The Appendixes include Appendix A. Search Strategy, Appendix B. Excluded Studies, Appendix C. Evidence Tables for Key Question 1, Appendix D. Evidence Tables for Key Question 2, and Appendix E. Evidence Tables for Key Question 3.

Methods

The methods for this systematic review follow those suggested in the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm).

Topic Refinement and Review Protocol

This topic was initially nominated through the public website and was subsequently refined with input from Key Informants and public comment. We generated an analytic framework, preliminary Key Questions, and preliminary inclusion/exclusion criteria in the form of PICOTS (populations, interventions, comparators, outcomes, timing, and settings). These processes were guided by a literature scan and information provided by the topic nominator, and were consistent with the Key Informant and public feedback. A Technical Expert Panel (TEP) was convened for this report. The TEP consisted of a group of nine scientists and clinicians, including individuals with expertise in transplant nephrology, infectious diseases, clinical pharmacology, and therapeutic drug monitoring and assay methodology. TEP members participated in conference calls and discussions through e-mail to review the scope, analytic framework, KQs, and PICOTS; provided input on the information and categories included in evidence tables; and provided input on the data analysis plan. A list of the TEP members will be included in the front matter of the final report. We drafted a protocol for developing this systematic review and finalized it in consultation with AHRQ and the TEP before it was posted on the Effective Health Care Web site on October 8, 2014. We note that one investigator who assisted with this review was also participating in a clinical study of an extended release formulation of tacrolimus. This formulation was not approved by the U.S. Food and Drug Administration (FDA) at the time our review was conducted, and therefore no studies of this drug were eligible for inclusion. In consultation with AHRQ we developed a risk mitigation plan to manage any potential conflict of interest.

Literature Search Strategy

Literature searches were performed by Medical Librarians and followed established systematic review protocols. Searches covered the literature published from January 1, 1994, through August 1, 2014. We chose 1994 as the earliest year because this reflects the timeframe in which the commonly used forms of calcineurin inhibitors (CNIs) received U.S. FDA approval. Tacrolimus (TAC) received approval in 1994 for use in liver transplants and in 1997 for use in renal transplants, and the modified formulation of cyclosporine A (CsA) received approval in 1995. Studies published before 1994 are likely to use formulations of CNIs no longer in common use.

Searches were restricted to English-language studies, given concerns that studies not published in English would be more likely to include clinical environments where post-transplant care, immunosuppressive therapy and clinical outcomes would vary substantially from standard practices in the United States, and given the abundance of English language studies identified in preliminary screening, including many studies conducted outside of the United States or Europe.

The following databases were searched using controlled vocabulary and text words: EMBASE, MEDLINE, PubMed, and the Cochrane Library. Our searches included strategies to identify studies "in process" that were not yet indexed. The search concepts and strategies are available in Appendix A.

We also searched 21 sources for gray literature not indexed in the bibliographic databases; these sources are detailed in Appendix A. In addition, the AHRQ Scientific Resource Center requested scientific information packets (SIPs) from relevant pharmaceutical and test manufacturing companies, asking for any unpublished studies or data relevant for this systematic review (SR). We received six documents listing completed studies conducted by three different manufacturers. These were assessed for inclusion in the review.

Literature screening was performed using the database Distiller SR (Evidence Partners, Ottawa, Canada). Literature search results were initially screened for relevancy. Relevant abstracts were then screened against the inclusion and exclusion criteria in duplicate. Due to the highly complex methods and results of the studies, those that appeared to meet the inclusion criteria were retrieved in full and screened in duplicate by clinical experts in transplant nephrology and pharmacology, to determine if they met the clinical criteria for inclusion. Studies that satisfied this first-pass full text screening were then screened by methodological experts for inclusion. All disagreements were resolved by consensus discussion among the two original screeners.

Study Selection

Table 2 below presents the study inclusion criteria that guided the selection of studies included in this report. The table is organized based on the PICOTS (patient, intervention, comparator, outcomes, timing, and setting) framework.

Table 2. Eligibility criteria

Category	Inclusion	Exclusion
Population	• Adult renal transplant recipients treated with full-dose or alternative dose calcineurin inhibitor (CNI) immunosuppression • All kidney donor types • Renal retransplant patients • Populations at increased risk of graft rejection	• Children (<18 years) • Multi-organ recipients
Interventions	Key Question 1a, 1b • High performance liquid chromatography (HPLC) • Liquid chromatography-tandem mass spectrometry (LC-MS/MS Key Question 2 • 2-hour postadministration monitoring of CsA (C2) Key Question 3 • CNI minimization strategies • CNI conversion strategies • CNI withdrawal strategies • CNI avoidance strategies	• Studies of investigational immunosuppressive agents that are not FDA approved, or studies using non-modified cyclosporine formulations • Studies designed to examine the effectiveness of an induction agent as a primary intervention • Studies using muromonab OKT3
Comparators	Key Question 1a, 1b • Fluorescence polarization immunoassay (FPIA) • Enzyme-multiplied-immunoassay techniques (EMIT) • Enzyme-linked immunosorbent assay (ELISA) • Microparticle enzyme immunoassay (MEIA) Key Question 2 • Trough monitoring of CsA (C0) Key Question 3	

Table 2. Eligibility criteria (continued)

Category	Inclusion	Exclusion
	• Full-dose CNIs • CNI minimization/conversion/withdrawal/avoidance strategies compared to each other	
Outcomes	**Key Question 1a, 1b** Analytical validity outcomes • Analytic accuracy (analytic sensitivity and specificity) • Analytic precision (e.g., intra-assay agreement, inter-assay agreement, measurement reproducibility) • Limit of quantification • Inter-laboratory comparisons (e.g., inter-laboratory agreement, measurement reproducibility) **All Key Questions** Intermediate-term clinical outcomes • Organ survival • Acute cellular and/or antibody mediated rejection (e.g. ascertained by "for cause" vs. "per protocol" biopsies) as defined by Banff criteria used in study • Chronic allograft injury (e.g. rejection or dysfunction, as defined by study) • Glomerular filtration rate (GFR), as measured by study • Serum creatinine • Infections (including timing of infections and clinical impact of infections on patients) • Malignancy • All-cause mortality • Immunosuppression regimen changed due to adverse events Adverse events • Acute and/or chronic nephrotoxicity (include GFR threshold method of measurement) • New-onset diabetes after transplant • Major adverse cardiac events • Other adverse outcomes (e.g., hyperkalemia, hypomagnesaemia, hyperuricemia, gastrointestinal complications, post-transplant hypertension or hyperlipidemia, proteinuria, hematologic side effects, neurologic complications, hair loss/gain) **Key Question 3** Long-term clinical outcomes • Health care utilization • Impact on provider workflow	
Timing	• At least 3-months post-transplant for Key Question 3	
Settings	• All settings where immunosuppressive therapy for transplant recipients is administered or monitored	
Publication Language	• English	

CNI=calcineurin inhibitors; CsA=cyclosporine; FDA=U.S. Food and Drug Administration; GFR=glomerular filtration rate

Data Extraction

Data were abstracted using Microsoft Word and Excel. Duplicate abstraction on a 10% random sample was used to ensure accuracy. All discrepancies were resolved by consensus discussion among the two original abstracters and an additional third person as needed. Elements abstracted included general study characteristics (e.g., country, study design, enrolled number of patients, special patient inclusion/exclusion criteria), patient characteristics (e.g., age, sex, donor type, delayed graft function), details of CNI monitoring method (e.g., type of analytic method used to measure CNI drug level, timepoint for monitoring), CNI treatment strategy (e.g., alternative CNI strategy, control strategy, induction agent), risk-of-bias items, and outcomes data.

Risk-of-Bias Assessment of Individual Studies

Risk of bias of the studies in Key Question 1 that compared the analytical validity of chromatographic techniques to immunoassays for monitoring CNI drug levels was assessed using eight risk-of-bias items. These items are based on an item bank developed in part by the EPC Program to evaluate the reporting adequacy and internal validity of studies evaluating the analytical validity of medical tests. The items were based on a review of other checklists and criteria used to assess the methodological quality of studies reporting on analytical validity, such as the criteria in the ACCE and EGAPPs approaches, and expert panel consensus. The full of the items and discussion of other methods used to assess studies of analytical validity can be found in the report titled *Addressing Challenges in Genetic Test Evaluation: Evaluation Frameworks and Assessment of Analytical Validity*.[18]

The eight items selected for this report broadly cover the following areas: adequate description of the tests under evaluation, reporting methods used to establish baseline performance of the tests, and reproducibility of the test results. When considering if a study adequately described the tests under evaluation, we looked to see if studies reported on how blood samples were collected and handled, if and how test materials were calibrated and tested, and if quality control/ assurance measures were used to evaluate samples. When considering methods used to establish baseline performance, we looked to see if studies reported on limit of detection and linearity range. Finally, when considering reproducibility, we looked to see if studies reported on the performance of the test over multiple testing times or across multiple laboratories. We discuss the limitations of the studies in the results section for Key Question 1.

For studies addressing clinical outcomes, we used ten items from an item bank that addresses the internal validity of comparative studies. This item bank was informed by empirical studies of the impact of study design on bias in comparative studies and is consistent with the guidance in AHRQ's "Methods Guide for Comparative Effectiveness Reviews."[19] Each item chosen addressed an aspect of study design or conduct that could help protect against bias, such as randomization of group assignment, or blinding outcome assessors to patient group assignment. Each item is phrased as a question that can be answered "Yes," "No," or "Not Reported," and each is phrased such that an answer of "Yes" indicates that the study reported a protection against bias on that aspect. The items used in this report are presented in Table E-21 of Appendix E. This table also presents the risk-of-bias ratings for all included studies.

Studies were rated as "Low," "Moderate," or "High" risk of bias. We identified three of the ten items as most indicative of potential bias: "Was randomization adequate?"; "Was allocation concealment adequate?"; and "Was there a <15 percent difference in completion rates in the

study's groups?" A study was rated as High risk of bias if any 2 of these 3 questions were answered "No" or "Not Reported". We considered the weight of the other seven items to be equal. Thus, if at least 2 of the more highly weighted criteria were answered "Yes," then a study was rated: as Low risk of bias if at least 75 percent of the total items were answered "Yes", as Moderate risk of bias if more than 50 percent but less than 75 percent were answered "Yes", and as High risk of bias if 50 percent or fewer of the items were answered "Yes."

Data Synthesis

For studies reporting on patient-centered clinical outcomes, we performed meta-analysis when appropriate and possible. Decisions about whether meta-analysis was appropriate depended on the judged clinical homogeneity of the different study populations, monitoring methods, CNI protocols, and outcomes. When meta-analysis was not possible (due to limitations of reported data) or was judged inappropriate, we synthesized the data using a descriptive, narrative approach.

We computed effect sizes and measures of variance using standard methods and performed random-effects meta-analysis using the Hartung-Knapp method.[20,21] Analyses were performed using the statistical software program R (GNU General Public License). For KQ 3, meta-analysis was performed on the following outcomes, as these were clinically important outcomes that were reported most consistently across studies: biopsy proven acute rejection (BPAR), graft loss, patient death, renal function, and infection-related adverse events, specifically: cytomegalovirus (CMV), BK virus infection, and other opportunistic infections. Renal function was measured by eGFR, which was assessed using a variety of commonly used analytical approaches, including the Modification of Diet in Renal Disease (MDRD) formula, the Nankivell formula, and the Cockcroft-Gault formula. Due to differences in how eGFR was measured across studies, data were pooled using the standardized mean difference (SMD) as the summary effect size metric. Due to the complex and heterogeneous nature of the studies addressing KQs 1 and 2, we did not attempt to combine data from the studies quantitatively. Instead, we provided a narrative synthesis of the general findings of the evidence addressing these questions.

For KQ 3, studies were categorized depending on the alternative CNI regimen they addressed: withdrawal, conversion, minimization, avoidance, and studies that compared alternative regimens head-to-head. Within each category of studies, subgroup analyses were performed. Subgroups were defined using the following criteria: type of CNI (CsA or TAC), type of immunosuppressant co-administered with the CNI, type of induction agent, and timing of initiation of alterative CNI strategy (<6 months vs. ≥6 months post-transplantation). We were unable to conduct subgroup analyses of kidney donor type or patients at higher risk for infections because studies rarely reported outcomes stratified by these criteria, and too few studies were identified that consisted entirely of these populations.

Results were considered to represent no difference for an outcome when the summary effect estimate was between 0.75 and 1.25 and the confidence interval included 1.0.

Strength of the Body of Evidence

For questions with clinical outcomes, we graded the strength of evidence based on the guidance established by the EPC program. Developed to grade the overall strength of a body of evidence, this approach incorporates five key domains: study limitations (includes study design and aggregate risk of bias), consistency, directness, precision, and reporting bias. It also considers optional domains, such as a dose-response association, plausible confounding that

would increase the observed effect, and strength of association (magnitude of effect), all of which may increase the strength of evidence. Table 3 defines the grades of evidence. We focused our assessment of the strength of evidence on studies reporting on clinical outcomes. We chose not to assess the strength of evidence for nonclinical outcomes reported in the studies of analytic validity (Key Questions 1a and 1b).

Table 3. Definitions of the grades of overall strength of evidence

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

We determined the study limitations by appraising the aggregate risk of bias of individual studies contributing to the evidence base for each comparison and clinical outcome. The evidence was downgraded when the risk of bias was judged to be high for 50 percent or more of the studies for a specific outcome.

We assessed consistency in terms of both the direction of effect and the magnitude of effect. Where quantitative synthesis was possible, the determination of inconsistency was based in part on the I^2 statistic. If I^2 was 50 percent or more, indicating the presence of substantial heterogeneity, we considered the evidence inconsistent. We downgraded the evidence for inconsistency unless the source of the heterogeneity was explained through subgroup analyses of identifiable differences in study characteristics.

The evidence was considered indirect if the populations, interventions, comparisons, or outcomes used within studies did not directly correspond to the comparisons we intended to evaluate. Evidence was downgraded for indirectness if a majority of studies in a specific outcome or a heavily weighted study in the summary effect size calculation met these criteria.

The evidence base was downgraded for imprecision if the 95% confidence intervals (CIs) surrounding the summary effect estimate for relative risk exceeded both a 10% increase in risk as well as a 10% decrease in risk. If the CIs exceeded a 25% increase and decrease in risk, the evidence base was downgraded further due to substantial imprecision. When only a single study was identified for a specific outcome, the evidence base was also considered imprecise and downgraded. We treated exceptions as they arose.

Reporting bias includes publication bias, outcome reporting bias, and analysis reporting bias. Since many of the studies we reviewed were funded by pharmaceutical manufacturers, we explored publication bias through a review of funnel plots. We examined funnel plots for the primary comparisons in Key Question 3. We also considered outcome reporting bias for this report, particularly for the outcome of "Other Opportunistic Infections." Data ascertainment and reporting for this outcome can vary widely, with some studies describing many different types of infections, while other studies report only one or two types of infections. We suspected reporting bias if studies appeared to selectively report incidence of specific opportunistic infections when the data favored the intervention regimen.

Applicability

Applicability of studies was determined by evaluating characteristics of included patients and parameters used by the studies for drug dosing and measuring immunosuppressant level targets. Studies had limited generalizability when their patient populations were at high risk for poor outcomes or were not representative of important subgroups (such as patients >65 years old, retransplants, or African-Americans). Studies also had limited applicability when CNI drug doses or immunosuppressant target levels were not considered to be within conventional standards of care (as assessed by the clinical investigators contributing to this report.)

Peer Review and Public Commentary

A variety of external experts have been asked to provide peer review on this report. In addition, the draft report is posted on the AHRQ Web site (www.effectivehealthcare.ahrq.gov) for public review. We will compile all comments and address each one individually, revising the text as appropriate. AHRQ also will review the final report prior to publication. The dispositions of the comments are documented and will be published 3 months after publication of the report.

Results

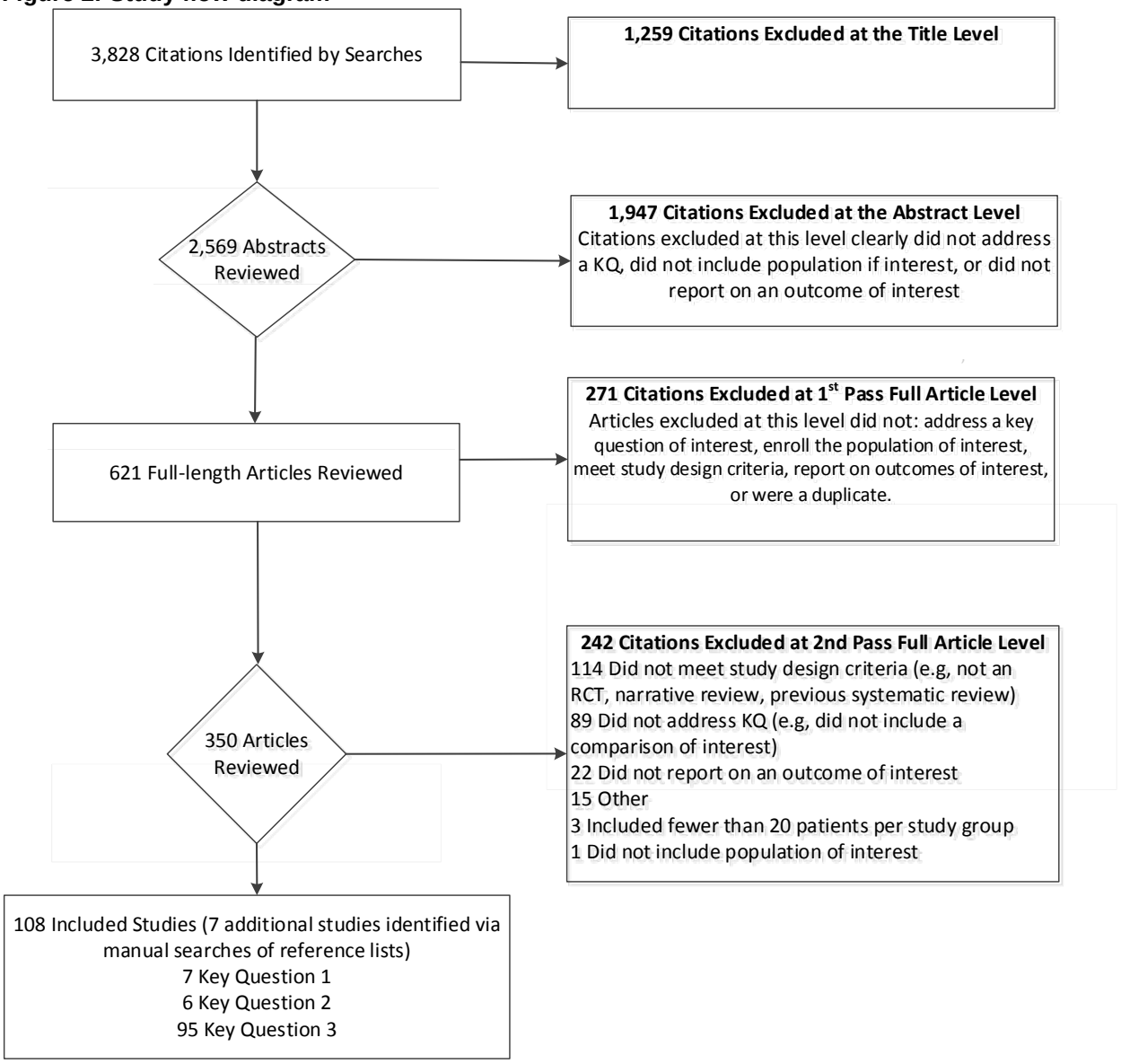
Introduction

We begin by describing the results of our literature searches. We then provide a brief description of the included studies. The remainder of the chapter is organized by Key Question. For each Key Question, we provide a detailed description of the studies, key summary points, a detailed analysis of the results, and a table that presents the strength of evidence.

Literature Searches

The literature searches identified 108 articles describing 97 randomized controlled trials (RCTs) (see Figure 2). Seven studies addressed Key Question (KQ) 1, and six studies examined KQ 2. The remaining 95 articles included 84 unique RCTs that addressed KQ 3. Among the 84 trials that addressed KQ 3, 32 examined reduced dosing of a calcineurin inhibitor (CNI), 20 evaluated converting from a CNI regimen to another immunosuppressive regimen, 13 assessed withdrawal of a CNI, 7 explored CNI avoidance through de novo use of non-CNI therapy, and 4 studies had more than 2 arms, which included a standard-dose CNI control group, a CNI minimization group, and either a conversion arm,[22] a withdrawal arm,[23,24] or an avoidance arm.[4] For these four multi-arm trials, data from each intervention group were analyzed with their respective regimens. Additionally, eight studies compared a low-dose CNI regimen with another type of alternative regimen without a standard-dose CNI arm to serve as a control group.

Figure 2. Study flow diagram



Methods for Monitoring CNI Drug Levels

Key Question 1a. How do liquid chromatographic and mass spectrometric analytical techniques compare with immunoassay analysis for therapeutic monitoring of full dosing regimens of CNIs?

Key Question 1b. How do liquid chromatographic and mass spectrometric analytical techniques compare with immunoassay analysis for therapeutic monitoring of lower dosing regimens of CNIs?

Immunoassays, such as microparticle enzyme immunoassay (MEIA) and enzyme-linked immunosorbent assay (ELISA), are commonly used to monitor CNI drug levels because they are relatively inexpensive, easy to use, and widely available. However, commercially available immunoassays use monoclonal antibodies that recognize not only the parent drug but also several of its metabolites. Cross-reactivity from CNI metabolites may lead to an overestimation of drug concentration, which could affect accurate interpretation of patient's drug levels and lead to less than optimal clinical outcomes. Compared with the immunoassays, high performance liquid chromatography (HPLC) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) offer more precise measures of the parent compound while minimizing measurement of metabolites. However, these methods are typically more expensive, time-consuming, labor-intensive, and less standardized, making them provider dependent. Currently, it is unclear whether clinical outcomes vary with different monitoring methods. And, given that CNI target ranges have decreased over time, it has become increasingly important to understand the ability of different measurement techniques to accurately quantify low-range CNI concentrations.

Description of Included Studies

We categorized studies that addressed this Key Question according to the "ACCE" framework, which identifies four important dimensions for evaluating a medical test: 1) Analytic validity; 2) Clinical validity; 3) Clinical utility; and 4) Ethical, legal and social implications. The first three of these criteria are meaningful for this Key Question. Analytical validity refers to how well a test measures the properties or characteristics it is intended to measure, in a laboratory setting. Clinical validity (or diagnostic accuracy) refers to the accuracy with which a test predicts the presence or absence of a clinical condition. Clinical utility refers to the usefulness of the test and the value of information to medical practice. Outcomes measured in support of clinical utility may range from impact on clinical thinking to impact on therapeutic decisions to patient health outcomes.

Overall, our literature searches identified seven studies that compared the use of chromatographic techniques to immunoassay techniques to measure CNI concentration levels. None of the studies evaluated clinical validity, but one of the studies assessed clinical utility. All of the identified studies examined the analytic validity of these tests to measure TAC concentration levels. Table 4 presents an overview of the studies addressing KQ 1.

The one study assessing clinical utility compared clinical outcomes among patients monitored with a chromatographic technique (i.e., HPLC-MS) versus an immunoassay.[25] The following clinical outcomes were evaluated: patient and graft survival, biopsy proven acute rejection (BPAR), cytomegalovirus (CMV) infection, TAC nephrotoxicity, and delayed graft

function. The remaining studies focused solely on the analytical validity of the different monitoring methods. The primary outcomes reported in these studies were analytic accuracy, bias, and precision. These outcomes and other measures of analytic performance reported in the studies are defined in Table 5. Due to the limited number of studies reporting on patient-level data and heterogeneity of the data on analytic performance, we did not attempt to pool data quantitatively. Instead, we narratively summarize key findings from the studies. Detailed information on study and patient-level characteristics, outcome data, and reported adverse events are presented in evidence tables in Appendix C.

Table 4. Methods used to measure CNIs

Reference	Type of Study	Monitoring Methods	Outcomes
Leung et al. 2014[26]	Prospective comparison of analytical performance of tests	LC-MS/MS vs. QMS TAC immunoassay (QMS)	Bias
Shipkova et al. 2014[27]	Prospective comparison of analytical performance of tests	LC-MS/MS vs. Elecsys TAC assay (ELCIA)	Bias
Westley et al. 2007[28]	Retrospective comparison of analytical performance of tests	HPLC-MS vs. CEDIA and MEIA	Bias
Borrows et al. 2006[25]	Randomized controlled trial	HPLC-MS vs. MEIA	Patient and graft survival, kidney function, biopsy proven acute rejection, TAC associated adverse events (e.g., TAC nephrotoxicity and CMV infection), and test precision.
Chan et al. 2005[29]	Prospective comparison of analytical performance	HPLC-MS vs. MEIA	Analytic accuracy
Staatz et al. 2002[30]	Retrospective comparison of analytical performance	LC-MS/MS vs. ELISA	Analytic accuracy and bias
Salm et al. 1997[31]	Prospective comparison of analytical performance	HPLC-MS vs. ELISA and MEIA	Analytic accuracy

CEDIA=Cloned enzyme donor immunoassay; CMV=cytomegalovirus; ELCIA=Electrochemiluminescence immunoassay; ELISA=Enzyme-linked immunosorbent assay; HPLC-MS=High performance liquid chromatography; LC/MS/MS=Liquid chromatography-tandem mass spectrometry; MEIA=Microparticle enzyme immunoassay; TAC=Tacrolimus

The risk of bias of the one RCT assessing clinical utility was rated as high due to the authors not reporting on the methods used to carry out the randomization procedure, and if the outcome assessors were blinded to patient assignment.

Findings for the risk-of-bias assessment of the analytic validity studies are presented in Table C-7. In general, most of the studies assessing analytic validity adequately described the tests under evaluation. However, the methods used to calibrate the tests and specifics about how the

blood samples were collected and handled varied across studies. Only two studies reported the limit of quantification of each test and the linearity range.[26,28] Similarly, only two studies reported that reproducibility was established prior to comparing the analytical performance of the tests.[26,27] One of these studies was a multicenter study in which reproducibility of the tests was established both over time and across participating laboratories.[27] None of the studies reported if the test interpreters were blinded to the testing methods used to monitor TAC levels.

Table 5. Measures of analytical performance

Term	Definition
Analytic accuracy	The analytic accuracy expresses the closeness of agreement between the true value (e.g., drug concentration) or an accepted reference value and the value found.
Precision	The degree to which the same method produces the same results on repeated measurements (repeatability and reproducibility); the degree to which values cluster around the mean of the distribution of values (i.e., the confidence limit).
Limits of Quantification	The highest or lowest concentration at which the drug can be reliably detected.
Linearity	The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of drug or analyte in the sample.
Bias	The mean (overall) difference in values obtained with two different methods of measurement.
Confidence Limit	Range within which 95% of the differences from the bias are expected to be.
Limits of Agreement (LOA)	Confidence limits for the bias. Upper limit of agreement is computed as bias + 1.96 standard deviation (SD). The lower limit of agreement is computed as bias − 1.96 SD. The range between the upper LOA and lower LOA is the confidence limit.

Source: http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm052377.pdf

Key Points

- One small study with high risk of bias reported on clinical validity outcomes. The evidence from this study was considered insufficient to permit conclusions about the comparative performance of HPLC versus immunoassay for clinical outcomes, due to limitations in methodological quality of the study and imprecision of the findings.
- The findings of the studies assessing analytical performance suggest that chromatographic methods are more analytically accurate and precise than commonly used immunoassays at measuring TAC drug levels, but it was unclear if differences identified in these studies were clinically relevant such that they would change clinical management or affect patient outcomes.

Summary of Clinical Utility Outcomes

Borrows et al. conducted an RCT comparing the clinical outcomes of renal transplant recipients in whom TAC trough concentration levels were monitored using HPLC versus MEIA.[25] Table 6 below presents the findings and strength of evidence ratings for the outcomes assessed in this study. Overall, the findings are insufficient to permit conclusions about the comparative performance of HPLC versus immunoassay for clinical outcomes.

Table 6. Key question 1. Strength of evidence ratings for clinical utility outcomes

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
HPLC vs. MEIA	Biopsy-proven acute rejection	Inconclusive (RR: 0.25; 95% CI: 0.02 to 2.14)	1 RCT[25] N=80	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (too few events) (0/40 versus 0/40)	1 RCT[25] N=80	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 0.33; 95% CI: 0.01 to 7.94)	1 RCT[25] N=80	Study Limitations Imprecision	Insufficient
	Serum creatinine levels (as measured using the Cockcroft Gault formula)	Inconclusive (SMD: 0.024, 95% CI: -0.41 to 0.43)	1 RCT[25] N=80	Study Limitations Imprecision	Insufficient
	Biopsy proven acute TAC nephrotoxicity	Inconclusive (RR: 0.85; 95% CI: 0.32 to 2.33)	1 RCT[25] N=80	Study Limitations Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 1.0, 95% CI: 0.49 to 2.04)	1 RCT[25] N=80	Study Limitations Imprecision	Insufficient
	Delayed graft function	Inconclusive (RR: 1.16; 95% CI: 0.62 to 2.20)	1 RCT[25] N=80	Study Limitations Imprecision	Insufficient

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations; Precision; and Directness. Consistency was not assessed as the evidence base included only one study. Publication and reporting bias were not assessed due to insufficient number of studies.CI=Confidence interval; HPLC-MS=High-performance liquid chromatography; MEIA=Microparticle enzyme immunoassay; RR=Relative risk; SMD=Standardized mean difference

Summary of Analytical Performance Outcomes

All seven studies addressing Key Question 1 compared the analytical performance of chromatographic techniques to an immunoassay. Three studies compared HPLC to either MEIA or CEDIA, two studies compared LC-MS/MS to either ELISA or MEIA, and two studies compared LC-MS/MS to TAC-specific immunoassays. Most of the studies had an adequate number of participants and blood samples (30 or more participants with close to or over 100 blood samples). The overall agreement between the chromatographic and immunoassay tests across all the studies was good (Pearsons's correlation estimate: r^2 range 0.90 to 0.97). The most commonly reported outcomes among these studies were analytic accuracy, bias, and precision. The key findings from these studies are summarized in Table 7.

In brief, three studies compared the analytic accuracy of chromatographic techniques to immunoassay to measure TAC at various concentration levels.[29-31] Only two of these studies adequately reported sufficient details about the methods used to calibrate the tests or how blood samples were obtained and managed.[29,31] Only one study reported on the limit of quantification.[29] None of these studies were multicenter studies, and none of them reported on whether reproducibility of the tests was established either within blood samples or across test operators or overtime. In general, the findings of these studies suggested that HPLC and LC-MS/MS were more accurate than an immunoassay in measuring TAC at lower concentration levels. However, it is unclear if these differences are clinically relevant such that they would

change clinical management or effect patient outcomes. We did not grade the strength of evidence for these nonclinical outcomes.

Four studies reported on bias between immunoassays compared to chromatographic techniques.[26-28,30] Three of the studies sufficiently reported details about the tests and also reported on other important aspects of conducting analytical validity studies, such as the linearity and reproducibility of the tests.[26-28] The remaining study did not provide any details about how tests were calibrated or samples were obtained or handled. It also did not report on other details such as linearity and reproducibility.[30] The results of these studies suggest that immunoassays overestimate TAC levels when compared to measurements from chromatographic techniques. We did not grade the strength of evidence for these nonclinical outcomes.

Finally, one RCT compared the precision of chromatographic techniques to immunoassays.[25] The findings of the study suggest that assay precision was better for HPLC-MS than MEIA. We did not grade the strength of evidence for this nonclinical outcome. Again, it is unclear if the differences found in these studies would change clinical management.

Table 7. Key findings of studies comparing analytic performance of chromatographic techniques versus immunoassays

Outcome	Quantity and Type of Evidence	Key Findings
Analytic accuracy	2 prospective and 1 retrospective comparative studies[29-31]	HPLC and LC-MS/MS more accurate than immunoassay at measuring TAC at lower concentration levels. --TAC concentration levels measured by HPLC-MS were statistically lower than levels measured by MEIA (median difference -0.40 (2.03) µg/L; p<0.001). --Concentration measurements of TAC at 5 ng/mL, 10 ng/mL, and 20 ng/mL had corresponding relative difference in values between LC-MS/MS and immunoassay (as expressed by 95% confidence intervals) of between -50% to 60%, -24% to 31%, and -11% to 17% --Measurement of TAC samples at various concentrations (1.0, 4.0, 15.0 and 50.0 µg/l), indicated acceptable accuracy of HPLC-MC at all levels tested (<10% deviation), and for ELISA at 1.0 and 4.0. Analytic accuracy was not acceptable for ELISA at 15.0 and 500 or for MEIA at all concentrations.
Bias	2 prospective and 2 retrospective comparative studies[26-28,30]	Compared to chromatographic techniques, bias for immunoassays ranged from 2.0 to 37%
Precision	1 RCT[25]	Inter-assay variability using Abbott Diagnostic control samples of 5, 11, and 22 ng/ml TAC was 8.0, 6.5, and 5.7 percent for HPLC-MS, respectively, compared to 13.7, 8.3, and 10.9 percent for MEIA, respectively

CEDIA=Cloned enzyme donor immunoassay; ELCIA=Electrochemiluminescence immunoassay; RCT=randomized controlled trial; ELISA=Enzyme-linked immunosorbent assay; HPLC-MS=High performance liquid chromatography; LC/MS/MS=Liquid chromatography-tandem mass spectrometry; MEIA=Microparticle enzyme immunoassay; TAC=Tacrolimus

Applicability

The majority of the studies addressing Key Question 1 were laboratory studies comparing the analytical performance of immunoassays to chromatographic techniques. These studies varied in terms of the quality controls used to prepare and handle blood samples, methods of calibrating equipment, and analytical methods used to process data. Such differences may limit the generalizability of the studies. Further, most of these studies took place in academic medical centers in which there was access to chromatographic technologies. Access to these technologies may be limited in smaller clinical settings.

Summary

Only one study at high risk of bias assessed clinical outcomes of renal recipients in whom TAC levels were measured with either a commonly used commercial immunoassay (e.g. MEIA) or HPLC. The evidence from this study was considered insufficient to permit conclusions about the comparative performance of HPLC versus immunoassay for clinical outcomes, due to limitations in methodological quality of the study and imprecision of the findings.

The findings of the studies assessing analytical performance suggest that chromatographic methods are more analytically accurate and precise than commonly used immunoassays at measuring CNI drug levels. However, the methodological quality of some of the studies is questionable due to not reporting information about baseline test characteristics such as limit of detection, linearity, and reproducibility, and it was unclear whether differences identified in these studies were clinically relevant such that they would change clinical management or affect patient outcomes.

Timing for Monitoring CNI Drug Levels

Key Question 2. How does two-hour post-administration CsA monitoring (C2) compare with trough monitoring (C0)?

Description of Included Studies

Overall, six comparative trials addressed this question. All but one study compared trough monitoring (C0) of CsA to 2-hour post-dose monitoring (C2) among new renal transplant recipients. The remaining study compared C0 monitoring to C2 monitoring of CsA among stable renal transplant recipients (>3 months post-transplant).[32] Due to the heterogeneous nature of the studies, we did not attempt to combine data from the studies quantitatively. Instead, we provide a narrative synthesis of the general findings of the studies. Detailed evidence tables presenting information on the design of the studies, study populations, findings, and risk-of-bias assessment are located in Appendix C.

Two of the included studies were RCTs. Both studies were rated as having high risk of bias. In one study, withdrawal was higher among patients in the C2 group (6 vs. 0 in C0 group) primarily due to discomfort of giving repeated blood samples. The other RCT was rated as having high risk of bias due to not reporting on randomization procedures, blinding of outcome assessors, or completion rates.

The remaining four studies were nonrandomized comparative trials. In general, these studies were rated as high risk of bias primarily due to not using methods to ensure group comparability, not reporting if outcome assessors were blinded, and retrospective designs.

Key Points

- Among new renal transplant recipients, risk of BPAR is similar between patients monitored at C0 and those monitored at C2. (Strength of Evidence: Low)
- Among new renal transplant recipients (within 20 days after transplant), evidence from one RCT indicated that C2 monitoring led to a significantly higher CsA mean cumulative dose increase compared to C0 monitoring. (Strength of Evidence: Low)
- Among new renal transplant recipients, evidence from one RCT demonstrated that significantly more patients in the C2 group experienced tremors than patients in the C0 group. (Strength of Evidence: Low)
- Among new renal transplant recipients, there was insufficient evidence available to draw conclusions about the association of C0 vs. C2 monitoring for the outcomes of patient and graft loss, renal function, and other adverse events. This was due to the study limitations and imprecision of findings in the non-randomized trials available.
- Among stable renal transplant recipients at 3 or more months after transplant, C2 monitoring led to significantly more CsA dose reductions than C0 monitoring. (Strength of Evidence: Low)

Detailed Synthesis

Studies of New Renal Transplant Recipients

One RCT compared CsA C2 monitoring to C0 monitoring among new renal transplant patients. Kyllonen and colleagues randomly assigned 160 patients before transplantation to C0 monitoring or C2 monitoring for 20-days post-transplantation.[33] After transplantation, CsA levels in both study groups were monitored at both C0 and C2 timepoints. However, depending on the randomization, the values of one method were blinded until the end of the 20-day study period. After 20 days, all patients were continued with C0 monitoring only. Patients at higher immunologic risk (i.e., panel reactive antibodies [PRA] >30% and/or previous graft loss within 1 year for immunologic reasons) were excluded from the study. The target C0 level was 200 to 300 µg/L, and the target C2 level was 1,500 to 2,000 µg/L. However, despite dose adjustments, 72 percent of C2 monitored patients did not reach the C2 target range by day-3 post-transplant, and 45 percent did not reach the target range by day-5 post-transplant. In contrast, 5 percent of patients did not reach the C0 target range by day-5 post-transplant.

The difficulty in reaching C2 target levels in this study likely explains the highly significant differences observed in the mean CsA doses and blood levels between the two monitoring groups. Low strength of evidence from this study indicated that C2 monitoring led to a significantly higher overall increase in CsA dose compared to C0 monitoring. The mean CsA dose in the group randomly assigned to management based on C2 monitoring was 56 percent higher than in the group randomly assigned to management based on C0 monitoring (11,409 mg versus 7,256 mg, respectively), and the mean C0 and C2 blood levels were 98 percent and 55 percent higher in the C2 group than the C0 group. In the C0 group, the mean cumulative CsA dose increased by 7,175 mg compared to a cumulative increase of 8,460 mg in the C2 group ($p<0.01$). Such differences, however, did not lead to differences in overall acute rejection rate between the groups.

The remainder of the evidence for new renal transplant patients comes from four nonrandomized studies.[34-37] Overall, low strength of evidence from these studies and the RCT suggests no difference in the risk of acute rejection between patients monitored at C2 and those at C0 (RR 0.95, 95% CI 0.61 to 1.45). One small non-RCT did demonstrate a significant decline in renal function among patients in the C0 group compared to those in the C2 group over the course of the study.[34] The serum creatinine level at 36 months was significantly higher among patients in the C0 group (1.46±0.52) than in patients in the C2 group (0.99±0.13, $p=0.04$). Similarly, creatinine clearance levels were significantly lower in the C0 group (55.15±19.21) than the in the C2 group (84.65±14.97, $p<0.001$). Patients in this study were followed for 36 months compared to 6 or fewer months in the other studies. For the most part, the evidence for patient and graft loss and adverse events among studies comparing C0 to C2 monitoring in new renal transplants was inconclusive due to study limitations of nonrandomized trials and imprecision of findings. However, low strength evidence from one RCT did indicate that significantly more patients in the C2 group (n=9) than in the C0 group (n=2) experienced tremors (RR 4.82, 95% CI 1.09 to 21.78).

Studies of Stable Renal Transplant Recipients

Jirasiritham and colleagues conducted an RCT comparing CsA C0 monitoring to C2 monitoring among patients who had more than 3 months of successful renal transplantation with well-functioning renal grafts.[32] The authors randomly assigned 35 patients to convert from C0

monitoring to C2 monitoring and 35 to remain on C0 monitoring. All patients were followed for 3 months. The target C2 level among patients converted to C2 monitoring was 800 ng/mL with 10% variation, and the target C0 level among patients who remained on C0 monitoring was 100 to 150 ng/mL. Lack of precision due to the study's small sample size and small number of events occurring in each group prevented conclusions for the primary outcomes of interest: acute rejection, patient and graft loss, and nephrotoxicity. The findings of the study did, however, provide low strength of evidence indicating that C2 monitoring led to more dosage reductions than C0 monitoring (34.3% vs. 14.3%, p=0.02). The discrepancy of the findings related to CsA dose between this study and the study by Kyllonen may be due to differences between the studies in the time period examined post-transplant. In the Kyllonen study, the patients were 20 days post-transplant, whereas in this study they were 3 or more months post-transplant. CsA levels tend to be more variable shortly after transplantation, and reaching target levels is often difficult.

Applicability

The applicability of the studies addressing this KQ is limited due primarily to the exclusion of patients at high risk of rejection. Overall, 71 percent of the studies excluded patients considered high risk. This includes patients over the age of 65 and patients with previous renal transplants. The average age range of patients enrolled in the studies was between 32 to 51 years. Few studies reported on race. Among the three studies that did, the majority of patients were Caucasian.

Summary

Table 8 presents the strength of evidence ratings for the studies addressing this KQ. Overall, low strength of evidence suggests that risk of BPAR is similar between new renal transplants monitored at C0 compared to those monitored at C2. For the most part, the evidence for patient and graft loss and adverse events among studies comparing C0 to C2 monitoring in new renal transplants was inconclusive due to study limitations of nonrandomized trials and imprecision of findings. However, low strength of evidence from one RCT indicated that C2 monitoring led to a significantly higher CsA mean cumulative dose increase compared to C0 monitoring. Low strength of evidence from this same study also indicated that significantly more patients in the C2 group than in the C0 group experienced tremors. In contrast, low strength of evidence from one small RCT indicated that C2 monitoring led to significantly more CsA dose reductions than C0 monitoring among stable renal recipients. The discrepancy of the findings related to CsA dose could be due to the difference in time post-transplant of patients in the studies. In one study, the patients were only 20 days post-transplant, whereas in the other study they were 3 or more months post-transplant. It is also possible that the difference reflects the fact that these conclusions come from single studies and that additional studies could overturn their conclusions.

Table 8. Key question 2. Strength of evidence ratings

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
C2 vs. C0 among new renal transplant recipients	BPAR	No difference (RR: 0.95; 95% CI: 0.61 to 1.45)	1 RCT, 3 non-RCTs[35-37] N=851	Study Limitations Imprecision	Low
	Patient death	Inconclusive (RR: 1.71; 95% CI: 0.41 to 7.05)	1 RCT, 2 non-RCTs[33,36,37] N=431	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 0.84; 95% CI: 0.33 to 2.14	1 RCT, 2 non-RCTs[35-37] N=635	Study Limitations Imprecision	Insufficient
	Serum creatinine levels	The findings from 1 non-RCT indicated serum creatinine level at 36 months was significantly higher among patients in the C0 group (1.46 ±0.52) than the C2 group (0.99 ± 0.13, p=0.04), and creatinine clearance levels were significantly lower in the C0 group (55.15±19.21) than the C2 group (84.65±14.97, p<0.001).	1 non-RCT[34] N=37	Study Limitations Imprecision	Insufficient
	CsA dosage	Findings from 1 RCT indicated significantly higher CsA mean cumulative dose increase among patients in the C2 group compared to the C0 group (8460 mg versus 7175 mg, p<0.01)	1 RCT[33] N=154	Study Limitations Imprecision	Low
	Chronic allograft nephrotoxicity (CAN)	Inconclusive (RR: 0.16; 95% CI: 0.02–1.09)	1 non-RCT[34] N=37	Study Limitations Imprecision	Insufficient
	Tremors	Findings from 1 RCT indicated significantly more patients in the C2 group (n=9) had tremors than the C0 group (n=2); (RR 4.82, 95% CI 1.09– 21.78)	1 RCT[33] N=154	Study Limitations Imprecision	Low
	Other Adverse Events	Inconclusive for other AEs (infections, cardiac symptoms, new onset diabetes)	1 RCTs, 2 non-RCTs[35-37] N=635	Study Limitations Imprecision	Insufficient

Table 8. Key question 2. Strength of evidence ratings (continued)

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
C2 vs. C0 among stable renal transplant recipients	BPAR	Inconclusive (RR: 0.33: 95% CI: 0.01–7.90)	1 RCT[32] N=70	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (no events)	1 RCT[32] N=70	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (no events)	1 RCT[32] N=70	Study Limitations Imprecision	Insufficient
	CsA dosage	C2 monitoring led to more dosage reductions compared to C0 monitoring (34.3% vs. 14.3%, p=0.02).	1 RCT[32] N=70	Study Limitations Imprecision	Low
	Nephrotoxicity	Inconclusive (no events)	1 RCT[32] N=70	Study Limitations Imprecision	Insufficient

The following factors were assessed for potential effect on the strength of evidence: Study Limitations; Precision; Consistency; and Directness. Publication and reporting bias not assessed due to insufficient number of studies. C2=2-hour CsA monitoring; CI=Confidence interval; CO=Trough monitoring; RCT=Randomized controlled trial; RR=Relative risk

Alternative CNI Regimens

Key Question 3a. In adult renal transplants, how do immunosuppressive regimens designed to reduce or eliminate exposure to CNI toxicity compare with each other and with full dose CNI regimens for health outcomes?

Key Question 3b. How does the type of induction agent (including when no induction is used,) and the use of concurrent immunosuppressive agents, impact outcomes of regimens that reduce or eliminate CNI exposure?

Regimens designed to reduce or eliminate CNI exposure after renal transplant were grouped into four types of strategies, as described in Table 1: minimization, conversion, withdrawal, and avoidance. Each regimen type was analyzed separately, and the head-to-head studies were assessed as a separate category.

The average age of renal transplant recipients enrolled in the studies was between 30 and 55 years. Thirty-five studies (42%) excluded patients over 75 years old, including 19 (23%) that excluded patients older than 65. Among studies reporting on patient race, the majority of enrolled patients were Caucasian males. Measures of patient socioeconomic status were not reported. In most studies, the majority of patients received their renal transplant from a deceased donor, although 11 studies (13%) enrolled only patients whose renal transplant was from a living donor. Sixty-seven studies (80%) were conducted in the United States or Europe, while others took place in Australia, Brazil, China, Egypt, India, Iran, Japan, Korea, Mexico, and New Zealand.

In general, the studies we reviewed excluded patients at high risk for graft failure or other adverse outcomes. Clinical indications commonly used to exclude participants included active infections, history of malignancies, prior renal transplant, and/or severe metabolic or hematologic abnormalities. In thirty-three studies (39%), patients with PRA greater than 50% were excluded, and retransplants were not eligible for participation in 21 studies (25%). Additionally, we excluded studies conducted in multi-organ transplant populations from our analysis.

Minimization

Description of Included Studies: Minimization

The most widely studied strategy reported in the RCTs identified by the literature search is minimization of CNI dosage. Minimization is most frequently implemented by reducing the target blood levels that are used to adjust dosing. CNI minimization has been evaluated for both CsA and TAC. CNI minimization has been supplemented with many combinations of other immunosuppressive drugs and induction agents. Thirty-six RCTs examining dose minimization met the inclusion criteria for this review (Table 9). Twenty-two studies used reduced dosing of CsA, seven studies examined TAC minimization, and seven RCTs combined populations that received CsA or TAC. Mycophenolic acid formulations (MMF or EC-MPS) were used as the primary additional immunosuppressive drug in 19 studies, and 14 studies used mammalian target of rapamycin (mTOR) inhibitors in addition to CNI. Two studies incorporated multiple adjunct therapies, including mycophenolic acid formulations, mTOR inhibitors, and azathioprine (AZA).

Vathsala[38] did not use any additional maintenance immunosuppressive therapy. Steroid therapy, usually prednisone, was administered in the intervention and control groups in nearly every study.

Induction therapy was widely used in these trials. Sixteen studies included basiliximab induction, three used daclizumab, one used alemtuzumab, two included rabbit antithymocyte globulin (rATG), and one indicated that induction therapy was not standardized and varied according to the local practice of study sites. Two studies indicated that induction therapy was not used, while the remaining 11 studies did not report on induction. Subgroup analysis of regimens with induction agents was performed separately for studies using mycophenolic acid formulations and mTOR inhibitors.

CNI exposure was usually minimized immediately or shortly after transplant. Twenty-nine studies initiated minimization within the first 6 months following transplant, 3 trials waited at least 6 months, and 4 adopted this strategy 1 year or more after transplant. Subgroup analysis was conducted comparing early (i.e., first 6 months after transplant) and late (i.e., 6 months or later after transplant) minimization for patients receiving MMF or mycophenolate sodium (MPS). We did not examine timing of minimization for patients receiving mTOR inhibitors because minimization was initiated early in all but two studies.

Risk of bias was determined to be high for 17 of the 36 minimization studies. The detailed assessments of risk of bias are presented in Table E-21 in the Appendix. Sixteen studies were categorized as moderate risk, and three studies were assessed as low risk of bias. Incomplete descriptions of randomization and allocation concealment practices were common, and many studies did not sufficiently describe whether all eligible patients were enrolled. Additionally, data on patient adherence with drug therapy were rarely included in published results. Twenty-seven trials were funded by sources that could benefit financially from the study results, such as pharmaceutical manufacturers. Five studies were funded by sources that did not appear to have a financial interest in the outcomes, and four studies did not report source of funding.

Table 9. Minimization studies

Reference	CNI	Other Immunosuppression	N, Intervention	N, Control
Xu 2011[39]	CsA, TAC	MMF	20	18
Gaston 2009[40]	CsA, TAC	MMF	243	477
Spagnoletti 2009[41]	CsA, TAC	MMF	30	30
Ekberg 2007b[4]	CsA, TAC	MMF	800	390
Hernandez 2007[42]	CsA, TAC	MMF	160	80
Tang 2006[43]	CsA, TAC	MMF, AZA	18	16
Cai 2014[44]	CsA	MPS	90	90
Chadban 2013[45]	CsA	MPS	42	33
Etienne 2010[46]	CsA	MMF	106	102
Fangmann 2010[47]	CsA	MMF	75	73
Budde 2007[48]	CsA	MPS	44	45
Cibrik 2007[49]	CsA	MPS	75	66
Ekberg 2007a[24]	CsA	MMF	183	173
Ghafari 2007[50]	CsA	MMF	42	48
Frimat 2006[51,52]	CsA	MMF	70	31
Stoves 2004[53]	CsA	MMF	13	16
Pascual 2003[54]	CsA	MMF	32	32
de Sevaux 2001[55]	CsA	MMF	152	161

Table 9. Minimization studies (continued)

Reference	CNI	Other Immunosuppression	N, Intervention	N, Control
Chan 2012[56]	TAC	MPS	151	141
Kamar 2012[57]	TAC	MPS	45	47
Bolin 2008[58]	TAC	MMF, SRL, AZA	100	223
Holdaas 2011[22]	CsA, TAC	EVR	144	123
Chadban 2014[23]	CsA	EVR	30	47
Muhlbacher 2014[59]	CsA	SRL	178	179
Cibrik 2013[60]	CsA	EVR	556	277
Takahashi 2013[61]	CsA	EVR	61	61
Oh 2014[62]	CsA	EVR	67	72
Paoletti 2012[63]	CsA	EVR	10	20
Bertoni 2011[64]	CsA	EVR	56	50
Salvadori 2009[65]	CsA	EVR	143	142
Nashan 2004[66]	CsA	EVR	58	53
Bechstein 2013[67]	TAC	SRL	63	65
Langer 2012[68]	TAC	EVR	107	117
Chan 2008[69]	TAC	EVR	49	43
Lo 2004[70]	TAC	SRL	23	16
Vathsala 2005[38]	CsA	None	20	10

AZA=Azathioprine; CsA=Cyclosporine; EVR=Everolimus; MMF=Mycophenolate mofetil; MPS=Mycophenolate sodium; N=number of patients; SRL=Sirolimus; TAC=Tacrolimus

Key Points

- Minimization of CNI exposure through low-dose regimens is associated with improved renal function and lower risk of acute rejection and graft loss (Strength of Evidence: High).
- Regimens using mycophenolic acid formulations and CsA are associated with better renal function, lower risk of acute rejection (Strength of Evidence: Moderate), and lower risk of graft loss (Strength of Evidence: High). The evidence for minimization regimens using mycophenolic acid formulations and TAC suggests improvement in renal function (Strength of Evidence: High) but is insufficient to draw conclusions for the other outcomes.
- Regimens that include mTOR inhibitors and CsA are associated with improved renal function and no difference in acute rejection (Strength of Evidence: Moderate), but the evidence for mTOR inhibitors with TAC is insufficient.
- Induction with basiliximab, when used with mTOR inhibitors, is associated with better renal function (Strength of Evidence: High), lower risk of graft loss, and no difference in risk of acute rejection (Strength of Evidence: Moderate), but the evidence is insufficient to draw conclusions when basiliximab is used with mycophenolic acid formulations.
- Minimization with low-dose CNIs and mycophenolic acid formulations that are initiated within the first 6 months after renal transplant are associated with improved renal function (Strength of Evidence: Low), lower risk of graft loss (Strength of Evidence: Moderate), and lower risk of acute rejection and infection. (Strength of Evidence: High).
- Minimization initiated 6 months after transplant or later is associated with increased risk of acute rejection (Strength of Evidence: Low). The evidence is insufficient to draw conclusions for other clinical outcomes.

Detailed Synthesis – Minimization Studies

Analysis combining results from all 36 trials (see Table 10) found that CNI minimization was associated with improved renal function, reduced risk of acute rejection and graft loss, and lower incidence of CMV and other opportunistic infections (with the exception of BK virus infection, for which the evidence was inconclusive). No difference was observed for patient death.

The strength of evidence for these findings was high for renal function, acute rejection, graft loss, and other opportunistic infections, and moderate for patient death and CMV infection. The evidence for BK virus infection was insufficient based on the four studies that reported this outcome due to the small number of reported infections and substantial imprecision and inconsistency in results. A moderate amount of heterogeneity was identified for the outcomes eGFR and CMV infection, but this was due to the inclusion of diverse immunosuppressive regimens and the inclusion of high and low risk patients in these comprehensive comparisons. The effect estimate for patient death was imprecise, and the outcome of other infections was subject to reporting bias. Further analyses were conducted to separate studies according to type of adjunctive immunosuppressive therapy and choice of CNI.

Mycophenolic Acid-based Adjunctive Therapy

Similar results were found for the 19 studies that used CNI minimization with mycophenolic acid formulations. In general, renal function improved, as measured by eGFR, and risk of acute rejection, graft loss, CMV infection, and other infections were reduced. No difference was observed for patient death, and the two studies that reported BK infection did not yield sufficient evidence to support a conclusion. Of these 19 studies, 14 minimized CsA and 5 minimized TAC. Examination of these studies separately found high or moderate-strength evidence that low-dose CsA was associated with improved renal function, reduced risk of acute rejection and graft loss, and incidence of opportunistic infections. The evidence was inconclusive for patient death, CMV infection, and BK virus infection. Low-dose TAC was also associated with improved renal function, based on high-strength evidence, but the evidence for the other important clinical outcomes we analyzed was insufficient to support conclusions.

Subgroup analyses were performed to evaluate the effect of induction therapy and timing of minimization on outcomes. Five studies used basiliximab induction in addition to CNI minimization and mycophenolic acid formulations. The evidence for each outcome was insufficient to support a conclusion due mainly to substantial imprecision in the effect size estimates. Three studies used daclizumab in the minimization arm and no induction in the control group. These studies were associated with an improvement in eGFR and lower risk of graft loss, death, and infection. However, only reduced risk of graft loss and other opportunistic infections were supported by high strength evidence, while the other outcomes were supported by moderate or low-strength evidence. Additionally, the results for acute rejection were inconclusive due to insufficient evidence.

Nine studies did not use induction or did not report whether induction was used. Meta-analysis of these trials found that minimization without induction, or when no induction was reported, was associated with improved renal function and reduced risk for acute rejection, graft loss, and death. The evidence base was moderate strength for eGFR and acute rejection and low strength for graft loss and death. Analyses of infection outcomes were inconclusive.

Overall, regimens that included mycophenolic acid formulations and low-dose CNI resulted in better outcomes than standard-dose CNI regimens when induction therapy was not used, not reported, or incorporated daclizumab. Unfortunately, none of the RCTs that examined low-dose

CNI regimens used different induction strategies across the minimization arm, so direct within-study comparisons of the effects of different induction agents were not possible. Further research is necessary to clarify the effect of induction therapy in CNI minimization.

Fourteen studies initiated minimization within 6 months after transplant. These trials were associated with improvement in all outcomes, except death and BK virus infection, for which the data were insufficient to support a conclusion. In five studies that reduced CNI dose 6 months after transplant or later, low-strength evidence indicated a higher risk of acute rejection. For the other outcomes, the evidence base was insufficient. Although no studies were identified that directly compared early with late minimization, the evidence indicates that early initiation is associated with improved outcomes while later initiation may not confer benefit and may be associated with harm. Importantly, these studies used minimization as a planned strategy in randomized populations and did not initiate lower-dose regimens in response to specific patient needs. This evidence base cannot address the potential benefits or harms of later-stage minimization in transplant recipients who experience CNI toxicity or other adverse events.

mTOR Inhibitor-based Adjunctive Therapy

Fourteen RCTs used SRL or EVR with reduced-dose CNI. Analysis of these studies found moderate-strength evidence for improvement in renal function, and low-strength evidence suggesting no difference for risk of acute rejection and lower incidence of CMV infection. The evidence was insufficient for the other outcomes.

Meta-analysis of the trials that specifically used a low-dose CsA with an mTOR inhibitor resulted in moderate-strength evidence that suggested improved renal function and no difference for risk of acute rejection. Low-strength evidence suggested a reduced risk for graft loss and CMV infection, while the evidence was insufficient to draw conclusions about risk of death or other opportunistic infections. Only one of these studies reported on BK infection, but the authors found significantly fewer cases in the minimization group. Four studies used low-dose TAC with an mTOR inhibitor, but the evidence was insufficient for all outcomes due to substantial imprecision in the effect size estimates. The overall improvement in outcomes associated with low-dose CNI and mTOR inhibitors appears to be influenced by the studies that used CsA but not regimens based on TAC.

Induction therapy with basiliximab was employed in 10 of the trials that lowered CNI dosing and used SRL or EVR. Improved renal function and lower risk of graft loss was found in these studies, supported by moderate-strength evidence, and low-strength evidence suggested lower risk of CMV infection. No differences were observed for the risk of graft loss and death, and the evidence was insufficient to support conclusions for the outcomes of BK virus and other infections. In the three studies that did not use or did not report induction therapy in conjunction with mTOR inhibitors, the evidence base was insufficient for all outcomes.

Applicability

The patient populations included in these studies were generally at lower risk of adverse outcomes, based on clinical and demographic characteristics, and the findings may thus be less applicable to higher-risk patients. The average age of included patients was between 40 and 50, and the proportion of men in most studies was between 60 and 70 percent. Most of the studies excluded patients with PRA that exceeded a defined threshold (typically 50%), and patients over age 65 or 70 were frequently excluded, as were retransplant recipients.

Two additional features of these studies limit the applicability of our findings. First, "minimization" is not a uniform approach based on a single strategy for reducing CNI dosing, and studies varied in their selection of target levels. For example, CsA low-dose targets ranged from 25 to 50 ng/mL in some studies, and 80 to 120 ng/mL in other trials. Similarly, low-dose TAC was defined as a trough target of 1.5 to 3.0 ng/mL in one study, and 5 to 10 ng/mL in another, while other studies varied within these ranges. Therefore, the target levels compared in this analysis do not represent the effect of a particular low-dose regimen. Rather, the results indicate that reduced CNI dosage is associated with improved outcomes compared with nonreduced dosing. This review cannot identify a specific target range for minimization that is associated with better clinical outcomes.

A second, related consideration is that target ranges for therapeutic drug levels are goals that may not be achieved for every patient or even a majority of patients in a study. The appendix (Table E-3) presents data on the extent to which target levels were achieved in intervention and control groups. Wide variation existed in how this information was reported and in the achievement of targets. We considered the impact of this variation on heterogeneity when we assessed the strength of evidence. However, due to incomplete and inconsistent reporting of data on achievement of target levels, it was not possible to conduct subgroup analyses based on these factors.

Summary

Overall, high and moderate-strength evidence suggests that CNI minimization, through low-dose regimens, improves patient outcomes and does not increase adverse event rates. The benefits associated with minimization were observed for CsA and TAC, although the evidence for TAC was frequently insufficient, and for regimens that included mycophenolic acid formulations or mTOR inhibitors as adjunct immunosuppressive therapy. Induction agents did not clearly correlate with improved outcomes, and results for subgroup analyses of induction therapy varied by adjunct immunosuppression treatment. Timing of initiating minimization may be an important factor affecting outcomes. High strength of evidence indicated improved clinical outcomes were associated with early minimization but not late minimization. It is important to note that all of these findings may be less applicable to patients at higher risk for poor clinical outcomes.

Table 10. Strength of evidence table for all minimization studies

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
All reduced CNI vs. Standard	Renal function	Minimization associated with improved eGFR (SMD: 0.32; 95% CI: 0.22–0.41; I^2=60%)	24 RCTs[4,22,24,39,42-45,47,48,51,54-57,59,61,62,64-69] N=5,043	None	High
	BPAR	Minimization associated with reduced rejection (RR: 0.84; 95% CI: 0.75–0.95; I^2=19%)	35 RCTs[4,22-24,38-40,42-51,53-70] N=7,563	None	High
	Graft loss	Minimization associated with reduced graft loss (RR: 0.76; 95% CI: 0.61–0.94; I^2=12%)	36 RCTs[4,22-24,38-51,53-70] N=7,623	None	High
	Patient death	No difference (RR: 0.91; 95% CI: 0.72–1.14; I^2=0)	32 RCTs[4,22-24,38-40,42,44,45,47-51,53-63,65-70] N=7,215	Imprecision	Moderate
	CMV infection	Minimization associated with lower incidence of CMV (RR: 0.71; 95% CI: 0.55–0.92; I^2=57%)	19 RCTs[4,23,24,38,40,42,47,54,55,58-61,64-68,70] N=5,666	Study Limitations	Moderate
	BK infection	Inconclusive (RR: 0.68; 95% CI: 0.06–7.55; I^2=65%)	4 RCTs[40,54,60,68] N=1,841	Study Limitations Imprecision Inconsistency	Insufficient
	Other opportunistic infections	Minimization associated with lower incidence of other infections (RR: 0.76; 95% CI: 0.64–0.91; I^2=0)	13 RCTs[4,24,38,43,47,49,51,54,55,57,59,66,67] N=3,065	None	High

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations; Precision; Consistency; Directness; Reporting Bias.
BPAR= Biopsy proven acute rejection; CI=Confidence interval; CMV=Cytomegalovirus; CNI=Calcineurin inhibitor; CsA=Cyclosporine; eGFR=Estimated glomerular filtration rate; mTOR=Mammalian target of rapamycin; NS=Not significant; RCT=Randomized controlled trial; RR=Relative risk; SMD=Standardized mean difference; TAC=Tacrolimus

Table 11. Strength of evidence table for minimization studies with adjunctive use of mycophenolic acid formulations

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Reduced CNI (cyclosporine or tacrolimus) + mycophenolic acid formulations vs. Standard	Renal function	Minimization associated with improved eGFR (SMD: 0.32; 95% CI: 0.20–0.45; I^2=55%)	13 RCTs[4,24,39,42,44,45,47,48,51,54-57] N=3,178	None	High
	BPAR	Minimization associated with reduced rejection (RR: 0.80; 95% CI: 0.68–0.95; I^2=27%	18 RCTs[4,24,39,40,42,44-51,53-57] N=4,366	None	High
	Graft loss	Minimization associated with reduced graft loss (RR: 0.71; 95% CI; 0.56–0.90; I^2=5%)	19 RCTs[4,24,39-42,44-51,53-57] N=4,426	None	High
	Patient death	No difference (RR: 0.87; 95% CI: 0.66–1.15; I^2=0)	17 RCTs[4,24,39,40,42,44,45,47-51,53-57] N=4,158	Imprecision	Low
	CMV infection	Minimization associated with lower incidence of CMV (RR: 0.77; 95% CI: 0.62–0.95; I^2=36%)	7 RCTs[4,24,40,42,47,54,55] N=3,031	None	High
	BK infection	Inconclusive (RR: 0.55; 95% CI: 0.07–4.57; I^2=0)	2 RCTs[40,54] N=784	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Minimization associated with lower incidence of other infections (RR: 0.77; 95% CI: 0.61–0.98; I^2=7%)	8 RCTs[4,24,47,49,51,54,55,57] N=2,405	Reporting Bias	Moderate
Reduced cyclosporine + mycophenolic acid formulations vs. Standard	Renal function	Minimization associated with improved eGFR (SMD: 0.28; 95% CI: 0.10–0.46; I^2=58%)	10 RCTs[4,24,42,44,45,47,48,51,54,55] N=2,756	Inconsistency	Moderate
	BPAR	Minimization associated with reduced risk of acute rejection (RR: 0.88; 95% CI: 0.76–1.02); I^2=0)	14 RCTs[4,24,42,44-51,53-55] N=3,224	Imprecision	Moderate
	Graft loss	Minimization associated with reduced graft loss (RR: 0.70; 95% CI; 0.55–0.88; I^2=0)	14 RCTs[4,24,42,44-51,53-55] N=3,224	None	High
	Patient death	Inconclusive (RR: 0.80; 95% CI: 0.54–1.20; I^2=0)	13 RCTs[4,24,42,44,45,47-51,53-55] N=3,016	Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 0.86; 95% CI: 0.62–1.18; I^2=47%)	6 RCTs[4,24,42,47,54,55] N=2,311	Imprecision	Insufficient

Table 11. Strength of evidence table for minimization studies with adjunctive use of mycophenolic acid formulations (continued)

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
	BK infection	Inconclusive, no events observed	1 RCT[54] N=64	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Minimization associated with lower incidence of other infections (RR: 0.83; 95% CI: 0.64–1.07; I^2=0)	7 RCTs[4,24,47,49,51,54,55] N=2,313	Imprecision	Moderate
Reduced tacrolimus + mycophenolic acid formulations vs. Standard	Renal function	Minimization associated with improved eGFR (SMD: 0.42; 95% CI: 0.22–0.62; I^2=29%)	4 RCTs[4,42,56,57] N=1,814	None	High
	BPAR	Inconclusive (RR: 0.76; 95% CI: 0.40–1.43; I^2=56%)	4 RCTs[4,42,56,57] N=1,814	Imprecision Inconsistency	Insufficient
	Graft loss	Inconclusive (RR: 0.88; 95% CI: 0.32–2.46; I^2=47%)	5 RCTs[4,41,42,56,57] N=1,874	Imprecision	Insufficient
	Patient death	Inconclusive (RR: 1.00; 95% CI: 0.45–2.24; I^2=0)	4 RCTs[4,42,56,57] N=1,814	Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 0.64; 95% CI: 0.27–1.52; I^2=0)	2 RCTs[4,42] N=1,430	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.63; 95% CI: 0.01–49.02; I^2=5%)	2 RCTs[4,57] N=1,282	Imprecision	Insufficient

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations; Precision; Consistency; Directness; Reporting Bias.
BPAR= Biopsy proven acute rejection; CI=Confidence interval; CMV=Cytomegalovirus; CNI=Calcineurin inhibitor; CsA=Cyclosporine; eGFR=Estimated glomerular filtration rate; mTOR=Mammalian target of rapamycin; NS=Not significant; RCT=Randomized controlled trial; RR=Relative risk; SMD=Standardized mean difference; TAC=Tacrolimus

Table 12. Strength of evidence table for subgroup analyses of minimization studies with adjunctive use of mycophenolic acid formulations

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Induction subgroup: Basiliximab + reduced CNI + mycophenolic acid formulations	Renal function	Inconclusive (SMD: 0.42; 95% CI: -0.78–1.62; I^2=84%)	3 RCTs[45,48,56] N=456	Imprecision Inconsistency	Insufficient
	BPAR	Inconclusive (RR: 0.86; 95% CI: 0.57–1.30; I^2=0)	4 RCTs[45,48,49,56] N=597	Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 1.57; 95% CI: 0.61–4.07; I^2=0)	5 RCTs[41,45,48,49,56] N=657	Imprecision	Insufficient
	Patient death	Inconclusive (RR: 1.10; 95% CI: 0.16–7.43; I^2=0)	4 RCTs[45,48,49,56] N=597	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 1.14; 95% CI: 0.66–1.95; p=0.64)	1 RCT[49] N=141	Imprecision	Insufficient
Induction subgroup: no induction or not reported + reduced CNI + mycophenolic acid formulations	Renal function	Minimization with no induction or not reported associated with improved eGFR (SMD: 0.25; 95% CI: 0.05–0.45; I^2=9%)	6 RCTs[39,44,51,54,55,57] N=788	Study Limitations	Moderate
	BPAR	Minimization with no induction or not reported associated with lower risk of rejection (RR: 0.83; 95% CI: 0.74–0.95; I^2=0)	9 RCTs[39,40,44,50,51,53-55,57] N=1,627	Study Limitations	Moderate
	Graft loss	Minimization with no induction or not reported associated with lower risk of graft loss (RR: 0.79; 95% CI: 0.60–1.04; I^2=0)	9 RCTs[39,40,44,50,51,53-55,57] N=1,627	Study Limitations Imprecision	Low
	Patient death	Minimization with no induction or not reported associated with lower risk of death (RR: 0.81; 95% CI: 0.61–1.08; I^2=0)	9 RCTs[39,40,44,50,51,53-55,57] N=1,627	Study Limitations Imprecision	Low
	CMV infection	Inconclusive (RR: 1.01; 95% CI: 0.50–2.01; I^2=17%)	3 RCTs[40,54,55] N=1,097	Study Limitations Imprecision	Insufficient
	BK infection	Inconclusive (RR: 0.55; 95% CI: 0.07–4.57; I^2=0)	2 RCTs[54,71] N=784	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 1.08; 95% CI: 0.52–2.24; I^2=0)	4 RCTs[51,54,55,57] N=570	Study Limitations Imprecision	Insufficient

Table12. Strength of evidence table for subgroup analyses of minimization studies with adjunctive use of mycophenolic acid formulations (continued)

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Induction subgroup: daclizumab only in minimization group + reduced CNI + mycophenolic acid formulations	Renal function	Minimization with daclizumab induction associated with improved eGFR (SMD: 0.25; 95% CI: 0.05–0.44; I^2=54%)	3 RCTs[4,24,47] N=1,694	Inconsistency	Moderate
	BPAR	Inconclusive (RR: 0.58; 95% CI: 0.16–2.15; I^2=93%)	3 RCTs[4,24,47] N=1,694	Imprecision Inconsistency	Insufficient
	Graft loss	Minimization with daclizumab induction associated with lower risk of graft loss (RR: 0.53; 95% CI: 0.31–0.91; I^2=8%)	3 RCTs[4,24,47] N=1,694	None	High
	Patient death	Minimization with daclizumab induction associated with lower risk of death (RR: 0.65; 95% CI: 0.40–1.05; I^2=0)	3 RCTs[4,24,47] N=1,694	Imprecision	Low
	CMV infection	Minimization with daclizumab induction associated with lower incident of CMV infection (RR: 0.81; 95% CI: 0.58–1.13; I^2=0)	3 RCTs[4,24,47] N=1,694	Imprecision	Low
	Other opportunistic infections	Minimization with daclizumab induction associated with lower risk of other infections (RR: 0.68; 95% CI: 0.50–0.94; I^2=0%)	3 RCTs[4,24,47] N=1,694	None	High
Early minimization subgroup: reduced CNI + mycophenolic acid formulations	Renal function	Early minimization associated with improved eGFR (SMD: 0.33; 95% CI: 0.16–0.45; I^2=61%)	10 RCTs[4,24,39,42,44,45,47,48,55,56] N=2,921	Study Limitations Inconsistency	Low
	BPAR	Early minimization associated with lower risk of rejection (RR: 0.79; 95% CI: 0.66–0.96; I^2=33%)	13 RCTs[4,24,39,40,42,44,45,47-50,55,56] N=3,872	None	High
	Graft loss	Early minimization associated with lower risk of graft loss (RR: 0.72; 95% CI: 0.54–0.95; I^2=9%)	14 RCTs[4,24,39-42,44,45,47-50,55,56] N=3,932	Study Limitations	Moderate
	Patient death	Inconclusive (RR: 0.87; 95% CI: 0.63–1.20; I^2=0)	13 RCTs[4,24,39,40,42,44,45,47-50,55,56] N=3,872	Study Limitations Imprecision	Insufficient
	CMV infection	Early minimization associated with lower risk of CMV (RR: 0.77; 95% CI: 0.61–0.96; I^2=39%)	6 RCTs[4,24,40,42,47,55] N=2,967	None	High

Table12. Strength of evidence table for subgroup analyses of minimization studies with adjunctive use of mycophenolic acid formulations (continued)

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
	BK infection	Inconclusive (RR: 0.53; 95% CI: 0.18–1.57; p=0.25)	1 RCT[40] N=720	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Early minimization associated with lower risk of other infections (RR: 0.76; 95% CI: 0.57–1.00; I^2=9%)	5 RCTs[4,24,47,49,55] N=2,148	Imprecision	Moderate
Late minimization subgroup: reduced CNI + mycophenolic acid formulations	Renal function	Inconclusive (SMD: 0.42; 95% CI: -0.17–1.02; I^2=6%)	3 RCTs[51,54,57] N=257	Imprecision	Insufficient
	BPAR	Late minimization associated with increased risk of acute rejection (RR: 1.48; 95% CI: 0.81–2.71; I^2=0)	5 RCTs[46,51,53,54,57] N=494	Imprecision	Low
	Graft loss	Inconclusive (RR: 0.62; 95% CI: 0.30–1.30; I^2=0)	5 RCTs[46,51,53,54,57] N=494	Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.87; 95% CI: 0.43–1.77; I^2=0)	4 RCTs[51,53,54,57] N=286	Imprecision	Insufficient
	CMV infection	Inconclusive, no events observed	1 RCT[54] N=64	Study Limitations Imprecision	Insufficient
	BK infection	Inconclusive, no events observed	1 RCT[54] N=64	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 2.35; 95% CI: 0.72–7.66; I^2=0)	3 RCTs[51,54,57] N=257	Imprecision	Insufficient

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations; Precision; Consistency; Directness; Reporting Bias.
BPAR= Biopsy proven acute rejection; CI=Confidence interval; CMV=Cytomegalovirus; CNI=Calcineurin inhibitor; CsA=Cyclosporine; eGFR=Estimated glomerular filtration rate; mTOR=Mammalian target of rapamycin; NS=Not significant; RCT=Randomized controlled trial; RR=Relative risk; SMD=Standardized mean difference; TAC=Tacrolimus

Table 13. Strength of evidence table for minimization studies with adjunctive use of mTOR inhibitors

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Reduced CNI (cyclosporine or tacrolimus) + mTOR inhibitors vs. Standard	Renal function	Minimization associated with improved eGFR (SMD: 0.31; 95% CI: 0.12–0.50; I^2=68%)	10 RCTs[22,59,61,62,64-69] N=1,831	Study Limitations	Moderate
	BPAR	No difference (RR: 0.95; 95% CI: 0.77–1.17; I^2=0)	14 RCTs[22,23,59-70] N=2,810	Study Limitations Imprecision	Low
	Graft loss	Inconclusive (RR: 0.79; 95% CI: 0.47–1.33; I^2=24%)	14 RCTs[22,23,59-70] N=2,810	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.97; 95% CI: 0.59–1.60; I^2=0)	13 RCTs[22,23,59-63,65-70] N=2,704	Imprecision	Insufficient
	CMV infection	Minimization associated with lower incidence of CMV (RR: 0.52; 95% CI: 0.29–0.93; I^2=55%)	10 RCTs[23,59-61,64-68,70] N=2,282	Study Limitations Inconsistency	Low
	BK infection	Inconclusive (RR: 0.84; 95% CI: 0.03–27.74; I^2=86%)	2 RCTs[60,68] N=1,057	Imprecision Inconsistency	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.75; 95% CI: 0.29–1.91; I^2=0)	3 RCTs[59,66,67] N=596	Study Limitations Imprecision	Insufficient
Reduced cyclosporine + mTOR inhibitors vs. Standard	Renal function	Minimization associated with improved eGFR (SMD: 0.36; 95% CI: 0.08–0.64; I^2=69%)	6 RCTs[59,61,62,64-66] N=1,120	Study Limitations	Moderate
	BPAR	No difference (RR: 0.88; 95% CI: 0.70–1.10; I^2=0)	9 RCTs[23,59-66] N=2,060	Imprecision	Moderate
	Graft loss	Minimization associated with reduced risk of graft loss (RR: 0.56; 95% CI: 0.26–1.18; I^2=31%)	9 RCTs[23,59-66] N=2,060	Imprecision	Low
	Patient death	Inconclusive (RR: 0.86; 95% CI: 0.42–1.77; I^2=0)	8 RCTs[23,59-63,65,66] N=1,954	Imprecision	Insufficient
	CMV infection	Minimization associated with reduced risk for CMV infection (RR: 0.51; 95% CI: 0.25–1.06; I^2=69%)	7 RCTs[23,59-61,64-66] N=1,891	Imprecision Inconsistency	Low
	BK infection	Minimization associated with reduced incidence of BK infection (RR: 0.15; 95% CI: 0.03–0.67; p=0.01)	1 RCT[60] N=833	Imprecision	Low
	Other opportunistic infections	Inconclusive (RR: 0.59; 95% CI: 0.15–2.30; I^2=30%)	2 RCTs[59,66] N=468	Study Limitations Imprecision	Insufficient

Table13. Strength of evidence table for minimization studies with adjunctive use of mTOR inhibitors (continued)

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Reduced tacrolimus + mTOR inhibitors vs. Standard	Renal function	Inconclusive (SMD: 0.37; 95% CI: -0.12–0.85; I^2=23%)	3 RCTs[67-69] N=444	Imprecision	Insufficient
	BPAR	Inconclusive (RR: 1.50; 95% CI: 0.78–2.91; I^2=0)	4 RCTs[67-70] N=483	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 0.88; 95% CI: 0.56–6.39; I^2=0)	4 RCTs[67-70] N=483	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 1.02; 95% CI: 0.31–3.35; I^2=0)	4 RCTs[67-70] N=483	Study Limitations Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 0.59; 95% CI: 0.21–1.65; I^2=0)	3 RCTs[67,68,70] N=391	Study Limitations Imprecision	Insufficient
	BK infection	Inconclusive (RR: 5.46; 95% CI: 0.65–45.99; p=0.12)	1 RCT[68] N=224	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.52; 95% CI: 0.10–2.72; p=0.43 for candida; RR: 1.03; 95% CI: 0.07–16.15; p=0.98 for herpes)	1 RCT[67] N=128	Study Limitations Imprecision	Insufficient

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations; Precision; Consistency; Directness; Reporting Bias.
BPAR= Biopsy proven acute rejection; CI=Confidence interval; CMV=Cytomegalovirus; CNI=Calcineurin inhibitor; CsA=Cyclosporine; eGFR=Estimated glomerular filtration rate; mTOR=Mammalian target of rapamycin; NS=Not significant; RCT=Randomized controlled trial; RR=Relative risk; SMD=Standardized mean difference; TAC=Tacrolimus

Table 14. Strength of evidence table for subgroup analyses of minimization studies with adjunctive use of mTOR inhibitors

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Induction subgroup: basiliximab + reduced CNI + mTOR inhibitors	Renal function	Induction with basiliximab associated with improved eGFR (SMD: 0.34; 95% CI: 0.10–0.58; I^2=61%)	7 RCTs[61,62,64-66,68,69] N=1,079	None	High
	BPAR	No difference (RR: 0.94; 95% CI: 0.77–1.14; I^2=0)	10 RCTs[23,60-66,68,69] N=2,019	Imprecision	Moderate
	Graft loss	Induction with basiliximab associated with reduced risk of graft loss (RR: 0.57; 95% CI: 0.32–1.03; I^2=28%)	10 RCTs[23,60-66,68,69] N=2,019	Imprecision	Moderate
	Patient death	No difference (RR: 0.97; 95% CI: 0.62–1.54; I^2=0)	9 RCTs[23,60-63,65,66,68,69] N=1,913	Imprecision	Low
	CMV infection	Induction with basiliximab associated with lower incidence of CMV infection (RR: 0.47; 95% CI: 0.20–1.09; I^2=62%)	7 RCTs[23,60,61,64-66,68] N=1,758	Imprecision Inconsistency	Low
	BK infection	Inconclusive (RR: 0.84; 95% CI: 0.03–27.74; I^2=86%)	2 RCTs[60,68] N=1,057	Imprecision Inconsistency	Insufficient
	Other opportunistic infections	Inconclusive for herpes simplex infections (RR: 0.13; 95% CI: 0.01–2.47; p=0.18)	1 RCT[66] N=111	Study Limitations Imprecision	Insufficient
Induction subgroup: no induction or not reported + reduced CNI + mTOR inhibitors	Renal function	Inconclusive (SMD: 0.26; 95% CI: -0.58–1.10; I^2=84%)	3 RCTs[22,59,67] N=752	Study Limitations Imprecision Inconsistency	Insufficient
	BPAR	Inconclusive (RR: 1.34; 95% CI: 0.22–8.08; I^2=64%)	3 RCTs[22,59,67] N=752	Study Limitations Imprecision Inconsistency	Insufficient
	Graft loss	Inconclusive (RR: 1.26; 95% CI: 0.21–7.50; I^2=0)	3 RCTs[22,59,67] N=752	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 1.20; 95% CI: 0.02–71.29; I^2=29%)	3 RCTs[22,59,67] N=752	Study Limitations Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 0.85; 95% CI: 0.10–7.30; I^2=0)	2 RCTs[59,67] N=485	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.78; 95% CI: 0.25–2.50; I^2=0)	2 RCTs[59,67] N=485	Study Limitations Imprecision	Insufficient

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations; Precision; Consistency; Directness; Reporting Bias.
BPAR= Biopsy proven acute rejection; CI=Confidence interval; CMV=Cytomegalovirus; CNI=Calcineurin inhibitor; CsA=Cyclosporine; eGFR=Estimated glomerular filtration rate; mTOR=Mammalian target of rapamycin; NS=Not significant; RCT=Randomized controlled trial; RR=Relative risk; SMD=Standardized mean difference; TAC=Tacrolimus

Conversion

Description of Conversion Studies

Overall, 21 studies assessed the benefits and harms of converting from a CNI to another maintenance immunosuppressive regimen. The majority of the studies (n=16) evaluated conversion from a CNI to an mTOR-based inhibitor (SRL or EVR). The other studies assessed conversion from CNI to AZA, MMF, MPS, or belatacept. Table 15 presents the immunosuppressive regimens assessed in the studies. In most of the studies, conversion took place within 3- to 6-months post-transplantation. Additional information about the dosing of the regimens is provided in Table E-5.

All the studies evaluating the impact of conversion were RCTs in which all patients were initially on a CNI regimen and then randomly assigned to either remain on the CNI regimen or convert to another immunosuppressive agent. Overall, 86 percent of the studies were rated as having moderate risk of bias. In most cases, the sources of potential bias were due to not reporting if there was allocation concealment or if outcome assessors were blinded, differential loss to followup, and potential conflict of interest of the funding source. The majority of studies (95%) were either industry funded or did not report the funding source. Three studies were rated as having a low risk of bias.[72-74] These studies clearly reported allocation concealment and did not have differential loss to followup. See Table E-21 for risk-of-bias ratings.

Table 15. Conversion studies

Reference	Type of Intervention	N, Intervention	N, Control
Bensal 2013[72]	CNI to SRL	31	29
Holdaas 2011[22]	CNI to EVR	127	123
Weir 2011[75]	CNI to SRL	148	151
Schena 2009[76]	CNI to SRL	555	275
Watson 2005[74]	CNI to SRL	19	19
Chhabra 2013[77]	TAC to SRL	123	64
Silva 2013[78]	TAC to SRL	97	107
Heilman 2011[79]	TAC to SRL	62	60
Mjornstedt 2012[80]	CsA to EVR	102	100
Nafar 2012[81]	CsA to SRL	50	50
Guba 2010[82]	CsA to SRL	69	71
Bemelman 2009[83]	CsA to EVR or MPS	74	39
Lebranchu 2009[84]	CsA to SRL	95	97
Durrbach 2008[85]	CsA to SRL	33	36
Barsoum 2007[86]	CsA to SRL	76	37
Budde 2012[73,92]	CsA to EVR	155	146
Bakker 2003[87]	CsA to AZA	60	68
MacPhee 1998[88]	CsA to AZA	102	114
Hilbrands 1996[89]	CsA to AZA	60	60
Dudley 2005[90]	CsA to MMF	73	70
Rostaing 2011[91]	CNI to belatacept	84	89

AZA=Azathioprine; CNI=Calcineurin Inhibitor; CsA=Cyclosporine; EVR=Everolimus; MMF=Mycophenolate mofetil; MPS=Mycophenolate sodium; SRL=Sirolimus; TAC=Tacrolimus

Key Points

- The overall risk of BPAR was higher among patients converted to an mTOR inhibitor (Strength of Evidence: High) or MPS (Strength of Evidence: Moderate) than those who remained on a CNI regimen.
- Patients converted to an mTOR inhibitor demonstrated modest improvement in renal function compared to patients who remained on a CNI regimen. (Strength of Evidence: Moderate)
- Patients converted to an mTOR inhibitor experienced fewer incidence of cytomegalovirus infection than patients remaining on a CNI regimen. (Strength of Evidence: High)
- Graft loss was similar among patients remaining on a CNI and those converting to an mTOR inhibitor or AZA. (Strength of Evidence: Low)
- The evidence was insufficient due to lack of precision to permit conclusions for the outcomes from studies that evaluated conversion from CsA to MMF.

Detailed Synthesis: Conversion Studies

All 16 studies evaluating conversion from a CNI regimen using either CsA or TAC to an mTOR-based regimen reported on the incidence of BPAR at 12-months following renal transplant. High strength of evidence suggested that the overall risk of BPAR was higher among patients converted to an mTOR inhibitor than patients who remained on a CNI regimen (RR: 1.35; 95% CI: 1.01 to 1.80). The results were similar when the analysis was stratified based on type of CNI inhibitor (CsA vs. TAC). Table 16 shows the findings and the strength-of-evidence ratings for BPAR and all other outcomes analyzed. Heterogeneity was low for the overall analysis of CNI versus conversion to an mTOR inhibitor and for the analyses for which CNIs were stratified by type.

A total of 15 studies contributed data to a pooled analysis comparing renal function as measured by glomerular filtration rate among patients converted to an mTOR inhibitor to renal function among those remaining on a CNI. Moderate strength evidence suggested modest improvement in renal function among those converted to an mTOR inhibitor (SMD: 0.38; 95% CI 0.11 to 0.64). When the analysis was stratified based on type of CNI, high strength evidence suggested improved renal function among those converted to an mTOR compared to patients remaining on CsA (SMD: 0.66; 95% CI: 0.20 to 1.12). However, low strength evidence indicated no difference in renal function between patients converted to an mTOR inhibitor and those remaining on TAC (RR: 0.88; 95% CI: 0.55 to 1.39).

Pooled analyses revealed substantial heterogeneity for renal function for both the overall CNI versus mTOR analysis (I^2= 89%) and the CsA versus mTOR sub-analysis (I^2= 88%). When the study by Barsoum and colleagues was removed from the analysis, the I^2 for the overall CNI analysis dropped to 74 percent and to 14 percent in the CsA subanalysis.[86] One primary difference between this study and the other studies in the analyses was a delay in the addition of MMF among patients converted to SRL from CsA. The addition of MMF among these patients occurred 3-months postconversion and 6-months post-transplant. In the other studies, MMF or MPS were initiated immediately or shortly after renal transplantation. This might explain why the between-group difference in eGFR was substantially higher in this study than the others.

The only other difference observed between patients converted to an mTOR inhibitor and those remaining on a CNI regimen was in the reported incidence of cytomegalovirus (CMV). High strength of evidence suggested that conversion to an mTOR inhibitor was associated with

lower reported incidence of CMV (RR: 0.61; 95% CI: 0.38 to 0.98; I^2=37%). This difference, however, was no longer present when the analysis was stratified by type of CNI (CsA versus TAC). Finally, low strength of evidence indicated no difference between groups in the overall CNI analysis or in the TAC sub-analysis in graft loss. The evidence was insufficient to draw any conclusions for patient death or other infection related adverse events among patients converted to an mTOR and those remaining on a CNI regimen.

Similarly, evidence from three studies that evaluated conversion from CsA to AZA was insufficient to support conclusions for the outcomes of acute rejection, patient death, and incidence of infection.[87-89] However, low strength of evidence from these studies did suggest that graft loss was similar among patients who converted to AZA and those who remained on CsA (RR: 0.84; 95% CI: 0.55 to 1.28, I^2=0).

Moderate strength evidence from one study in which patients were converted from CsA to MPS indicated a significantly higher risk of BPAR among patients converted to MPS.[83] In this study, eight patients in the MPS group experienced an episode of acute rejection compared to only one patient in the CsA group (RR: 8.61; 95% CI 1.14 to 65.9; p=0.04). The evidence was insufficient to permit conclusions for patient or graft loss or risk of infection among patients converted to MMF or MPS and those who remained on CsA.

Finally, the findings of one study in which patients were converted from CsA to belatacept showed a modest improvement in GFR among patients who converted to belatacept (60.5±11.01 mL/min/MDRD vs. 56.5±14.42 mL/min/MDRD; mean change from baseline 2.1±10.34, p<0.01). The evidence from this study was inconclusive for patient or graft loss or infection risk.

We did not conduct sub-group analyses of these studies to identify effects associated with induction agents. Induction therapy is expected to affect patient outcomes immediately after transplantation and shortly thereafter, but is less likely to have an impact during the later timeframes when most studies initiated CNI conversion. Moreover, sub-groups were too small for analysis due to heterogeneity and frequent non-reporting of induction therapy.

Applicability

The applicability of the findings of the studies assessing conversion from a CNI to another immunosuppression regimen is limited due to lack of reporting about key patient characteristics such as race and exclusion of patients considered high risk. Overall, 38 percent of the studies evaluating conversion did not report on race. Among those that did, the majority of the enrolled patients were male Caucasians. Thirteen studies (62%) excluded patients considered high risk. This includes older patients (≥65 years of age) and patients who had a previous renal transplant. Overall, 8 studies (38%) excluded patients aged 65 years or older, and 6 (28%) excluded patients who had a previous renal transplant.

Summary

Overall, there was high- to moderate strength of evidence suggesting that conversion from a CNI regimen to an mTOR inhibitor or MPS was associated with an increased risk of BPAR. Moderate -strength evidence also indicated that conversion to an mTOR inhibitor was associated with modest improvement in renal function. The strength of evidence was high for the finding that conversion to an mTOR was associated with a decreased risk in the incidence of CMV infection. Finally, low-strength evidence suggests no difference in graft loss between patients remaining on a CNI and those converting to an mTOR inhibitor or AZA. For patient death or incidence of other infection-related adverse events, the findings of our analyses were

inconclusive due to lack of precision. In general, the followup period in the majority of studies addressing conversion was relatively short (12 months) and limited primarily to low risk patients.

Table 16. Strength of evidence table for conversion studies

Comparison	Outcome	Conclusions	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
CNI (cyclosporine or tacrolimus) to mTOR inhibitors	BPAR	Conversion to mTOR associated with increased risk of BPAR (RR: 1.35; 95% CI: 1.01–1.80; I^2=23%)	16 RCTs[22,72,74-86,92] N=3,007	None	High
	Graft loss	No difference (RR: 1.03; 95% CI: 0.68–1.56; I^2=44%)	12 RCTs[22,75-80,82,84-86,92] N=2,878	Imprecision	Low
	Patient death	Inconclusive (RR: 1.20; 95% CI: 0.60–2.39; I^2=3%)	12 RCTs[22,75-80,82,84-86,92] N=2,878	Imprecision	Insufficient
	Renal function	Conversion to mTOR associated with improved renal function (SMD: 0.38; 95% CI: 0.11–0.64; I^2=89%)	15 RCTs[22,72,74-80,82,84-86,92] N=2,967	Inconsistency	Moderate
	CMV Infection	Conversion to mTOR associated with lower incidence of CMV (RR: 0.61; 95% CI: 0.38–0.98; I^2=37%)	10 RCTs[72,75,77-80,82,83,85,92] N=1,660	None	High
	BK infection	Inconclusive (RR: 0.59; 95% CI: 0.20–1.79; I^2=40%)	7 RCTs[72,75,77-80,84,92] N=1,332	Imprecision	Insufficient
	Other infection	Inconclusive (RR: 1.28; 95% CI: 0.84–1.97; I^2=28%)	10 RCTs[72,74-80,86,92] N=1,660	Imprecision	Insufficient
Tacrolimus to mTOR inhibitors	BPAR	Inconclusive (RR: 1.75; 95%CI: 0.35–8.08; I^2=0%)	3 RCTs[77-79] N=513	Imprecision	Insufficient
	Graft loss	No difference (RR: 0.88; 95% CI: 0.55–1.39; I^2=0%)	3 RCTs[77-79] N=513	Imprecision	Low
	Patient death	Inconclusive (RR: 1.46; 95% CI: 0.24–8.83; I^2=0%)	3 RCTs[77-79] N=513	Imprecision	Insufficient
	Renal function	No difference (SMD: -0.11; 95% CI: -0.47–0.25; I^2=0%	3 RCTs[77-79] N=513	Imprecision	Low
	CMV Infection	Inconclusive (RR: 0.70; 95% CI: 0.07–6.91; I^2=56%)	3 RCTs[77-79] N=513	Imprecision	Insufficient
	BK infection	Inconclusive (RR: 0.35; 95% CI: 0.11–1.14; I^2=0%)	2 RCTs[77,79] N=309	Study Limitations Imprecision	Insufficient
	Other infection	Inconclusive (RR: 0.58; 95% CI: 0.05–6.47; I^2=0%)	3 RCTs[77-79] N=513	Imprecision	Insufficient

Table 16. Strength of evidence table for conversion studies (continued)

Comparison	Outcome	Conclusions	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Cyclosporine to mTOR inhibitors	BPAR	Inconclusive (RR: 1.19; 95% CI: 0.71–1.98; I^2=48%)	8 RCTs[80-86,92] N=1,163	Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 0.91; 95% CI: 0.30–2.82; I^2=12%)	6 RCTs[80,82,84-86,92] N=986	Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.76; 95% CI: 0.38–1.55; I^2=0%)	6 RCTs[80,82,84-86,92] N=986	Imprecision	Insufficient
	Renal function	Conversion to mTOR associated with improved renal function (SMD: 0.66; 95% CI: 0.20–1.12; I^2=88%; with outlier study removed SMD: 0.48; 95% CI: 0.32–0.65; I^2=14%)	7 RCTs[80-84,86,92] N=1,094	None	High
	CMV infection	Inconclusive (RR: 0.56; 95% CI: 0.23–1.38; I^2=54%)	5 RCTs[80,82,83,85,92] N=788	Imprecision	Insufficient
	BK infection	Inconclusive (RR: 1.59; 95% CI: 0.33–7.61; I^2=0%)	3 RCTs[80,84,92] N=534	Imprecision	Insufficient
	Other infection	Inconclusive (RR: 1.30; 95% CI: 0.28–6.11; I^2=57%)	3 RCTs[80,84,92] N=534	Imprecision	Insufficient
Cyclosporine to azathioprine	BPAR	Inconclusive (RR: 0.93; 95% CI: 0.52–1.68; I^2=0%)	3 RCTs[87,89,89] N=464	Study Limitations Imprecision	Insufficient
	Graft loss	No difference (RR: 0.84; 95% CI: 0.55–1.28; I^2=0%)	3 RCTs[87,89,89] N=464	Study Limitations Imprecision	Low
	Patient death	Inconclusive (RR: 0.92; 95% CI: 0.41–2.04; I^2=14%)	3 RCTs[87,89,89] N=465	Study Limitations Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 3.35; 95% CI 0.13–82.5)	1 RCT[89] N=120	Study Limitations Imprecision	Insufficient

Table 16. Strength of evidence table for conversion studies (continued)

Comparison	Outcome	Conclusions	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Cyclosporine to mycophenolic acid formulations	BPAR	Conversion to MPS associated with higher incidence of acute rejection (RR: 8.67; 95% CI: 1.14–65.9)	1 RCTs[83] N=103	Imprecision	Moderate
	Graft loss	Inconclusive (RR: 0.473, 95% CI 0.09–2.50)	1 RCT[90] N=143	Imprecision	Insufficient
	Patient death	Inconclusive (too few events) (RR: 7.0, 95% CI 0.36–133)	1 RCT[90] N=143	Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 1.62; 95% CI 0.20–12.9; I^2=0%)	2 RCTs[83,90] N=256	Imprecision	Insufficient
CNI (cyclosporine or tacrolimus) to Belatacept	BPAR	Inconclusive (RR: 13.76, 95% CI 0.78–240)	1 RCT[91] N=173	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (no events) (0/84 vs. 0/89)	1 RCT[91] N=173	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.35, 95% CI 0.01–8.54)	1 RCT[91] N=173	Study Limitations Imprecision	Insufficient
	Renal function	Inconclusive (SMD: 0.31; 95% CI -0.02–0.64)	1 RCT[91] N=173	Study Limitations Imprecision	Insufficient
	CMV infection	Inconclusive (too few events) (RR: 1.06, 95% CI 0.15–7.35)	1 RCT[91] N=173	Study Limitations Imprecision	Insufficient
	BK infection	Inconclusive (too few events) (RR: 7.41, 95% CI 0.39–141)	1 RCT[91] N=173	Study Limitations Imprecision	Insufficient
	Other infection	Inconclusive (RR: 1.06, 95% CI 0.22–5.10)	1 RCT[91] N=173	Study Limitations Imprecision	Insufficient

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations; Precision; Consistency; Directness; Reporting Bias.

BPAR=Biopsy proven acute rejection; CI=Confidence interval; CMV=Cytomegalovirus; CNI=Calcineurin inhibitor; eGFR=Estimated glomerular filtration rate; mTOR=Mammalian target of rapamycin; RCT=Randomized controlled trial; RR=Relative risk; SMD=Standardized mean difference

Withdrawal

Description of Withdrawal Studies

Renal transplant patients on a CNI-based regimen may benefit from having CNI withdrawn, while continuing alternative immunosuppression therapies. Withdrawal is different from conversion because the non-CNI immunosuppressive agent is included in the regimen before withdrawal, while conversion strategies do not introduce the alternative drug until discontinuation of the CNI.

Fifteen RCTs examined CNI withdrawal (Table 17). Nine studies included MMF as the primary alternative to CNI, and six studies used mTOR inhibitors. CsA was withdrawn in 10 studies (6 with MMF and 4 with SRL or EVR). TAC was withdrawn in two studies that used SRL. Three studies that used MMF combined data on patients receiving the CNIs CsA or TAC. Seven studies included fewer than 100 patients, while the largest study enrolled 430 transplant recipients. Nine studies initiated withdrawal within 6 months following transplant, 5 studies withdrew CNI 6 months or more post-transplant, and 1 study began withdrawal between 2 and 16 months after renal transplant.

Overall risk of bias was assessed as high for 10 of the withdrawal studies, moderate for 4 studies, and one study was at low risk of bias.[93] Only 1 study declared funding support from a noncommercial source,[94] 2 studies did not disclose any funding information,[95,96] and 12 of the 15 studies received funding from sources that could benefit financially from favorable study results.

Table 17. Withdrawal studies

Reference	Withdrawn	Maintained	N, Intervention	N, Control
Mourer 2012[97]	CNI	MMF	79	79
Pascual 2008[93]	CNI	MMF	20	20
Suwelack 2004[98]	CNI	MMF	18	20
Asberg 2012[99]	CsA	MMF	20	19
Ekberg 2007a[24]	CsA	MMF	179	173
Hazzan 2006[94]	CsA	MMF	54	54
Abramowicz 2002[100]	CsA	MMF	85	85
Schnuelle 2002[96]	CsA	MMF	44	40
Smak Gregoor 2002[101]	CsA	MMF	63	149
Chadban 2014[23]	CsA	EVR	49	47
Stallone 2003[95]	CsA	SRL	20	20
Gonwa 2002[102]	CsA	SRL	100	97
Johnson 2001[103]	CsA	SRL	215	215
Flechner 2011[104]	TAC	SRL	152	139
Freitas 2011[105]	TAC	SRL	23	24

CNI=Calcineurin inhibitor; CsA=Cyclosporine; EVR=Everolimus; MMF=Mycophenolate mofetil; SRL=Sirolimus; TAC=Tacrolimus

Key Points

- Withdrawal was associated with increased risk of acute rejection for patients maintained on mycophenolate acid formulations (Strength of Evidence: High) or mTOR inhibitors (Strength of Evidence: Moderate).

- Risk of graft loss was higher when CNI was withdrawn from patients remaining on MMF (Strength of Evidence: Low). The evidence for the outcome of graft loss was insufficient to support conclusions for studies that maintained patients on mTOR inhibitors (Strength of Evidence: Insufficient).
- Maintenance of MMF after CNI withdrawal was associated with improvement in renal function (Strength of Evidence: High)
- The evidence base is insufficient to support conclusions for the risk of infections in patients withdrawn from CNIs.

Detailed Synthesis of Withdrawal Studies

Withdrawal of CNI therapy was associated with increased risk of BPAR, regardless of whether patients received MMF or mTOR inhibitors as the primary alternative immunosuppressive agent. High-strength evidence demonstrated a large magnitude of effect, with risk of rejection more than three times greater in patients maintained on MMF after CNI withdrawal compared with recipients continued on both MMF and CNI. A smaller but still significant effect was observed in regimens using mTOR inhibitors, with a relative risk of rejection greater than 1.7. Risk of graft loss was also higher when CNI was withdrawn from patients remaining on MMF based on low-strength evidence, but the evidence base was inconclusive for this outcome in studies that maintained patients on mTOR inhibitors after CNI withdrawal.

High-strength evidence also supported the finding that maintenance of MMF after CNI withdrawal was associated with improvement in renal function, but the evidence for eGFR was inconclusive for the subset of studies using CsA. Evidence for other outcomes, including infections and death, was insufficient to support conclusions.

Timing of withdrawal with respect to renal transplant was assessed in subgroup analyses of the nine studies that included MMF, since all six studies that used mTOR inhibitors used early withdrawal. Three studies initiated CNI withdrawal during the first 6-months post-transplant (designated “early withdrawal”), and five studies initiated withdrawal 6 months or later after transplant (“late withdrawal”). One study included both early and late withdrawal.[93] Low-strength evidence was found for improved renal function in the late withdrawal subgroups. Early withdrawal was associated with higher risk of graft loss and death, and the evidence was insufficient to make conclusions for acute rejection and renal function. For studies of late withdrawal, maintenance of MMF after CNI withdrawal was associated with greater risk of acute rejection based on moderate-strength evidence. The evidence was insufficient to support any conclusions regarding infection outcomes in these subgroups.

We did not conduct sub-group analyses of these studies to identify effects associated with induction agents. As with conversion strategies, induction therapy is not expected to have a clinically significant impact during the later timeframes when most studies initiated CNI withdrawal. Moreover, sub-groups were too small for analysis due to heterogeneity and frequent non-reporting of induction therapy.

Applicability

The studies of CNI withdrawal have similar limits on applicability as described elsewhere. Nine of the 15 studies excluded patients who exceeded a defined PRA threshold. In 10 studies that reported patient race, at least three-quarters of participants were Caucasian. These studies

are therefore most applicable to average or low-risk patients. However, only one study excluded patients over 65 years old, and just 1 study excluded retransplants. Moreover, seven studies reported the proportion of patients who experienced DGF, which was present in at least 13% of intervention group patients in each study.

Summary

High strength evidence based on 15 RCTs indicates that CNI withdrawal is associated with greater risk of acute rejection for renal transplant recipients (Table 18). Moderate-strength evidence suggests that withdrawal may be associated with increased graft loss in patients maintained on MMF. Renal function may improve after withdrawal in some patients, and the evidence base is inconclusive for death and infection outcomes.

Table 18. Strength-of-evidence table for withdrawal studies

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
CNI withdrawal + mycophenolate	Renal function	Withdrawal associated with improved renal function (SMD: 0.49; 95% CI: 0.26–0.72; I^2=21%)	5 RCTs[24,93,96,97,106] N=742	None	High
	BPAR	Withdrawal associated with higher risk of rejection (RR: 3.17; 95% CI: 1.78–5.66; I^2=46%)	9 RCTs[24,93,96-101,106] N=1,201	None	High
	Graft loss	Withdrawal associated with higher risk of graft loss (RR: 1.35; 95% CI: 0.80–2.26; I^2=0)	9 RCTs[24,93,96-101,106] N=1,201	Imprecision	Low
	Patient death	No difference (RR: 0.99; 95% CI: 0.67–1.48; I^2=0)	8 RCTs[24,93,96,97,99-101,106] N=1,163	Imprecision	Low
	CMV infection	Inconclusive (RR: 1.12; 95% CI: 0.39–3.21; I^2=22%)	5 RCTs[24,93,96,98,101] N=726	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.73; 95% CI: 0.47–1.12; I^2=35%)	5 RCTs[24,93,96,98,101] N=726	Imprecision	Insufficient
Cyclosporine withdrawal + mycophenolate	Renal function	Inconclusive (SMD: 0.54; 95% CI: -0.07–1.15; I^2=54%)	3 RCTs[24,96,106] N=544	Study Limitations Imprecision Inconsistency	Insufficient
	BPAR	Withdrawal associated with higher risk of rejection (RR: 3.23; 95% CI: 1.39–7.47; I^2=60%)	6 RCTs[24,96,99-101,106] N=965	Study Limitations Inconsistency	Low
	Graft loss	Withdrawal associated with higher risk of graft loss (RR: 1.56; 95% CI: 0.95–2.54; I^2=0)	6 RCTs[24,96,99-101,106] N=965	Study Limitations Imprecision	Low
	Patient death	Inconclusive (RR: 1.11; 95% CI: 0.66–1.87; I^2=0)	6 RCTs[24,96,99-101,106] N=965	Study Limitations Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 1.49; 95% CI: 0.26–8.62; I^2=41%)	3 RCTs[24,96,101] N=648	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.73; 95% CI: 0.31–1.69; I^2=54%)	3 RCTs[24,96,101] N=648	Imprecision Inconsistency	Insufficient

Table 18. Strength-of-evidence table for withdrawal studies (continued)

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Early withdrawal subgroup: CNI + mycophenolate	Renal function	Early withdrawal associated with improved renal function (SMD: 0.54; 95% CI: -0.07–1.15; I^2=54%)	3 RCTs[24,96,106] N=544	Study Limitations Imprecision Inconsistency	Insufficient
	BPAR	Inconclusive (RR: 1.69; 95% CI: 0.59–4.85; I^2=26%)	3 RCTs[24,96,106] N=544	Study Limitations Imprecision	Insufficient
	Graft loss	Early withdrawal associated with higher risk of graft loss (RR: 1.34; 95% CI: 0.75–2.39; I^2=0)	3 RCTs[24,96,106] N=544	Study Limitations Imprecision	Low
	Patient death	Early withdrawal associated with higher risk of death (RR: 1.45; 95% CI: 0.87–2.40; I^2=0)	3 RCTs[24,96,106] N=544	Study Limitations Imprecision	Low
	CMV infection	Inconclusive (RR: 0.98; 95% CI: 0.04–21.99; I^2=0)	2 RCTs[24,96] N=436	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.60; 95% CI: 0.11–3.22; I^2=0)	2 RCTs[24,96] N=436	Study Limitations Imprecision	Insufficient
Late withdrawal subgroup: CNI + mycophenolate	Renal function	Late withdrawal associated with improved eGFR (61.1 vs. 52.9, p<0.01;[97] 66 vs. 63, p=NS;[100] increase of 4.5 mL/min, p=0.16[101])	3 RCTs[97,100,101] N=540	Imprecision	Low
	BPAR	Late withdrawal associated with higher risk of rejection (RR: 6.16; 95% CI: 3.11–12.21; I^2=0)	5 RCTs[97-101] N=617	Imprecision	Moderate
	Graft loss	Inconclusive (RR: 1.40; 95% CI: 0.33–5.95; I^2=0)	5 RCTs[97-101] N=617	Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.83; 95% CI: 0.37–1.83; I^2=0)	4 RCTs[97,99-101] N=579	Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 0.83; 95% CI: 0.05–13.36; I^2=80%)	2 RCTs[98,101] N=250	Study Limitations Imprecision Inconsistency	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.98; 95% CI: 0.08–11.73; I^2=0)	2 RCTs[98,101] N=250	Study Limitations Imprecision	Insufficient

Table 18. Strength-of-evidence table for withdrawal studies (continued)

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
CNI withdrawal + mTOR inhibitors	Renal function	Inconclusive (SMD: 0.16; 95% CI: -0.25–0.57; I^2=70%)	5 RCTs[23,95,103-105] N=904	Study Limitations Imprecision Inconsistency	Insufficient
	BPAR	Withdrawal associated with higher risk of rejection (RR: 1.71; 95% CI: 1.19–2.45; I^2=5%)	6 RCTs[23,95,102-105] N=1,101	Study Limitations	Moderate
	Graft loss	Inconclusive (RR: 0.97; 95% CI: 0.45–2.09; I^2=30%)	6 RCTs[23,95,102-105] N=1,101	Study Limitations Imprecision	Insufficient
	Patient death	No difference (RR: 1.03; 95% CI: 0.64–1.66; I^2=0)	6 RCTs[23,95,102-105] N=1,101	Study Limitations Imprecision	Low
	CMV infection	Inconclusive (RR: 0.91; 95% CI: 0.01–119.68; I^2=0)	2 RCTs[23,103] N=526	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.68; 95% CI: 0.39–1.18; p=0.17)	1 RCT[103] N=430	Study Limitations Imprecision	Insufficient
Cyclosporine withdrawal + mTOR inhibitors	Renal function	Inconclusive (SMD: 0.26; 95% CI: -0.71–1.23; I^2=71%)	3 RCTs[23,95,103] N=566	Study Limitations Imprecision Inconsistency	Insufficient
	BPAR	Withdrawal associated with higher risk of acute rejection (RR: 1.67; 95% CI: 0.87–3.22; I^2=22%)	4 RCTs[23,95,102,103] N=763	Study Limitations Imprecision	Low
	Graft loss	Withdrawal associated with lower risk of graft loss (RR: 0.64; 95% CI: 0.37–1.12; I^2=0)	4 RCTs[23,95,102,103] N=763	Study Limitations Imprecision	Low
	Patient death	Inconclusive (RR: 0.82; 95% CI: 0.39–1.74; I^2=0)	4 RCTs[23,95,102,103] N=763	Study Limitations Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 0.91; 95% CI: 0.01–119.68; I^2=0)	2 RCTs[23,103] N=526	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.68; 95% CI: 0.39–1.18; p=0.17)	1 RCT[103] N=430	Study Limitations Imprecision	Insufficient

Table 18. Strength-of-evidence table for withdrawal studies (continued)

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Tacrolimus withdrawal + mTOR inhibitors	Renal function	Inconclusive (SMD: 0.00; 95% CI: -2.48–2.48; I^2=43%)	2 RCTs[104,105] N=338	Study Limitations Imprecision	Insufficient
	BPAR	Withdrawal associated with higher risk of rejection (RR: 1.93; 95% CI: 1.43–2.60; I^2=0)	2 RCTs[104,105] N=338	Study Limitations	Moderate
	Graft loss	Inconclusive (RR: 2.15; 95% CI: 0.29–16.01; I^2=0)	2 RCTs[104,105] N=338	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 1.40; 95% CI: 0.31–6.19; I^2=0)	2 RCTs[104,105] N=338	Study Limitations Imprecision	Insufficient

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations; Precision; Consistency; Directness; Reporting Bias.
BPAR=Biopsy proven acute rejection; CI=Confidence interval; CMV=Cytomegalovirus; CNI=Calcineurin inhibitor; eGFR=Estimated glomerular filtration rate; mTOR=Mammalian target of rapamycin; NS=Not significant; RCT=Randomized controlled trial; RR=Relative risk; SMD=Standardized mean difference

Avoidance

Description of Avoidance Studies

Another strategy to prevent CNI-associated toxicity is complete avoidance of CNI regimens. Immunosuppressive treatment based on SRL or belatacept has been studied in eight RCTs (Table 19). Sirolimus was used with MMF in four studies, with AZA in one study, and alone in one study. Five of the SRL studies were small and included fewer than 150 patients each, while 1 study included nearly 800 patients.[4] Two large multinational trials, BENEFIT[107] and BENEFIT-EXT,[108] compared belatacept and MMF to CsA and MMF, with basiliximab induction in both groups. BENEFIT-EXT enrolled only extended criteria donors, who are typically associated with poorer clinical outcomes. Both BENEFIT studies included and compared more and less intensive schedules for administration of belatacept. We attempted to combine the BENEFIT studies for meta-analysis, but the results masked individual study effects and exhibited high heterogeneity, probably due to the differences in patient populations. Therefore, we report these two studies separately in the synthesis of results and the assessment of strength of evidence.

The six remaining studies used SRL, but one did not use an induction agent while the others varied widely in choice of induction, including basiliximab, alemtuzumab, daclizumab, and ATG. The studies also differed in whether induction was used solely in the intervention arm or in the control arm as well.

Five of the avoidance studies were assessed to have moderate risk of bias, while three were categorized as high risk of bias. Adherence with treatment regimen was of particular concern as a threat to validity in these studies, as four of eight studies did not achieve at least 85% adherence. Six studies were funded by sources with a commercial interest in the outcome, while two studies did not report a funding source.

Table 19. Avoidance studies

Reference	Intervention	Control	Induction	N, Intervention	N, Control
Vincenti 2010[107]	Belatacept, MMF	CsA, MMF	Basiliximab	445	221
Durrbach 2010[108]	Belatacept, MMF	CsA, MMF	Basiliximab	359	184
Flechner 2002[109]	SRL, MMF	CsA, MMF	Basiliximab	31	30
Ekberg 2007b[4]	SRL, MMF	CsA, MMF	Daclizumab (non-CNI arm)	399	390
Glotz 2010[110]	SRL, MMF	TAC, MMF	rATG (non-CNI arm)	71	70
Schaefer 2006[111]	SRL, MMF	TAC, MMF	ATG	41	78
Groth 1999[112]	SRL, AZA	CsA, AZA	None used	41	42
Refaie 2011[113]	SRL	TAC	Alemtuzumab	10	11

ATG=Anti-thymocyte globulin; AZA=Azathioprine; CNI=Calcineurin inhibitor; CsA=Cyclosporine; MMF=Mycophenolate mofetil; SRL=Sirolimus; TAC=Tacrolimus

Key Points

- The evidence base for these CNI avoidance regimens was small and mainly inconclusive.
- The studies were heterogeneous in their use of immunosuppressive therapies and induction agents.
- Belatacept was associated with improved renal function (Strength of Evidence: Moderate) and no difference in risk of graft loss or death. (Strength of Evidence: Low).

- Studies that used mTOR inhibitors and MMF instead of CNI were associated with improved renal function but higher risk of graft loss, compared with tacrolimus regimens (Strength of Evidence: Low), and no difference in risk of graft loss compared with cyclosporine regimens (Strength of Evidence: Low.) Results for the other outcomes were generally inconclusive.

Detailed Synthesis of Avoidance Studies

Each BENEFIT study found that belatacept was associated with improved renal function based on moderate-strength evidence, and low-strength evidence suggested it was noninferior to CsA for the outcomes of graft loss and death (Table 20). The study that used standard-criteria donors also found that belatacept was associated with increased risk for acute rejection, while the study conducted with extended-criteria donors found that belatacept was noninferior to CsA for this outcome. These studies did not provide sufficient evidence to draw conclusions for the infection outcomes.

Two studies compared SRL to CSA, with MMF in both arms.[4,109] SRL was associated with no difference in risk of graft loss, based on low-strength evidence. The evidence was insufficient to support conclusions for the other outcomes.

Two studies compared SRL to TAC, with MMF in both arms.[110,111] SRL was associated with improved renal function and lower risk of CMV infection, but a higher risk of graft loss, based on low-strength evidence. The evidence was insufficient to support conclusions for other outcomes.

Groth studied a regimen of SRL and AZA, compared with CsA and AZA, in 83 patients. Moderate- to low-strength evidence showed no difference in renal function or acute rejection and an increased risk of other opportunistic infections. The evidence was inconclusive for the outcomes of graft loss, death, and CMV infection.

Finally, a small study[113] of 21 kidney recipients compared SRL to TAC, with alemtuzumab induction in both groups but no additional immunosuppressive therapy. Renal function as measured by creatinine clearance was observed to improve in the SRL group; the evidence base for other outcomes was insufficient to draw conclusions.

We did not conduct sub-group analyses of these studies to identify effects associated with induction agents. Although induction therapy could be important in explaining differences in patient outcomes in these studies, sub-groups were too small for analysis.

Applicability

The BENEFIT-EXT study is one of few studies included in this report that specifically enrolled patients at higher risk for poor clinical outcomes. The other seven studies were similar to those described in the sections on CNI minimization, conversion, and withdrawal. Four studies excluded patients based on a PRA threshold, four excluded older patients, and two excluded retransplants. These studies are generally applicable to average or low-risk renal transplant recipients but may be limited in their generalizability to other populations.

Summary

Moderate- or low-strength evidence, based on a small number of heterogeneous studies, indicates that regimens that use belatacept or SRL from the time of transplant are associated with few differences in clinical outcomes compared with standard-dose CNI regimens.

Table 20. Strength-of-evidence table for avoidance studies

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Belatacept + MMF vs. CsA + MMF, with basiliximab induction in both groups, with standard-criteria donors	Renal function	Associated with improved eGFR ((Less intensive belatacept regimen: SMD: 0.55; 95% CI: 0.36–0.74; p<0.001); more intensive belatacept regimen: SMD: 0.58; 95% CI: 0.39–0.77; p<0.001)	1 RCT[107,108] N=666	Imprecision	Moderate
	BPAR	Associated with increased risk of acute rejection (RR: 2.73; 95% CI: 1.64–4.54; p<0.001)	1 RCT[107,108] N=666	Imprecision	Moderate
	Graft loss	Belatacept noninferior to CsA (RR: 0.56; 95% CI: 0.22–1.43; p=0.22)	1 RCT[107,108] N=666	Imprecision	Low
	Patient death	Belatacept noninferior to CsA (RR: 0.71; 95% CI: 0.27–1.84; p=0.48)	1 RCT[107,108] N=666	Imprecision	Low
	CMV infection	Inconclusive (RR: 0.78; 95% CI: 0.45–1.36; p=0.39)	1 RCT[107,108] N=666	Imprecision	Insufficient
	BK infection	Inconclusive (RR: 0.72; 95% CI: 0.31–1.65; p=0.44)	1 RCT[107] N=666	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.61; 95% CI: 0.33–1.14; p=0.12)	1RCT[107,108] N=666	Imprecision	Insufficient
Belatacept + MMF vs. CsA + MMF, with basiliximab induction in both groups, with extended-criteria donors	Renal function	More intensive belatacept regimen associated with improved eGFR (SMD: 0.32; 95% CI: 0.11–0.53; p<0.01); inconclusive for less intensive belatacept regimen (SMD: 0.18; 95% CI: -0.02–0.39; p=0.08)	1 RCT[108] N=543	Imprecision	Moderate
	BPAR	Belatacept noninferior to CsA (RR: 1.26; 95% CI: 0.83–1.92; p=0.28)	1 RCT[108] N=543	Imprecision	Moderate
	Graft loss	Belatacept noninferior to CsA (RR: 0.85; 95% CI: 0.50–1.43; p=0.53)	1 RCT[108] N=543	Imprecision	Low
	Patient death	Belatacept noninferior to CsA (RR: 0.77; 95% CI: 0.32–1.85; p=0.56)	1 RCT[108] N=543	Imprecision	Low
	CMV infection	Inconclusive (RR: 0.96; 95% CI: 0.61–1.53; p=0.87)	1 RCT[108] N=543	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.51; 95% CI: 0.23–1.12; p=0.09)	1 RCT[108] N=543	Imprecision	Insufficient

Table 20. Strength-of-evidence table for avoidance studies (continued)

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
mTOR inhibitors + mycophenolate mofetil vs. Cyclosporine + mycophenolate mofetil	Renal function	Inconclusive (SMD: 0.46; 95% CI: -0.53–1.45; I^2=92%)	2 RCT[4,109] N=850	Imprecision Inconsistency	Insufficient
	BPAR	Inconclusive (RR: 0.93; 95% CI: 0.31–2.81; I^2=58%)	2 RCT[4,109] N=850	Imprecision Inconsistency	Insufficient
	Graft loss	No difference (RR: 1.01; 95% CI: 0.64–1.59; I^2=0)	2 RCT[4,109] N=850	Imprecision	Low
	Patient death	Inconclusive (RR: 0.96; 95% CI: 0.46–2.04; I^2=0)	2 RCT[4,109] N=850	Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 0.58; 95% CI: 0.19–1.77; I^2=49%)	2 RCT[4,109] N=850	Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 0.82; 95% CI: 0.56–1.21; p=0.32)	1 RCT[4] N=789	Imprecision	Insufficient
mTOR inhibitors + mycophenolate mofetil vs. Tacrolimus + mycophenolate mofetil,	Renal function	Regimen associated with improved eGFR at 12 months (68 mL/min versus 62 mL/min; p=0.06)[110] and improved serum creatinine at 3 months (1.3 vs. 1.5, p=0.01)[111]	2 RCT[110,111] N=260	Study Limitations Imprecision	Low
	BPAR	Inconclusive (RR: 1.48; 95% CI: 0.76–2.86; I^2=0)	2 RCT[110,111] N=260	Study Limitations Imprecision	Insufficient
	Graft loss	Regimen associated with higher risk of graft loss (RR: 3.75; 95% CI: 1.26–11.13; I^2=0)	2 RCT[110,111] N=260	Study Limitations Imprecision	Low
	Patient death	Inconclusive (RR: 2.45; 95% CI: 0.49–12.29; I^2=7%)	2 RCT[110,111] N=260	Study Limitations Imprecision	Insufficient
	CMV infection	Regimen associated with lower incidence of CMV (RR: 0.07; 95% CI: 0.01–0.52; p=0.009)	1 RCT[110] N=141	Study Limitations Imprecision	Low
	BK infection	Inconclusive (RR: 4.93; 95% CI: 0.24–100.89; p=0.30)	1 RCT[110] N=141	Study Limitations Imprecision	Insufficient
	Other opportunistic infections	Inconclusive (RR: 1.77; 95% CI: 0.63–5.03; p=0.28)	1 RCT[110] N=141	Study Limitations Imprecision	Insufficient
mTOR inhibitors + azathioprine vs. Cyclosporine + azathioprine	Renal function	No difference (69.5±4.1 mL/min vs. 58.7±3.6 mL/min, p=NS)	1 RCT[112] N=83	Imprecision	Moderate
	BPAR	Inconclusive (RR: 1.09; 95% CI: 0.64–1.85; p=0.75)	1 RCT[112] N=83	Imprecision	Insufficient

Table 20. Strength-of-evidence table for avoidance studies (continued)

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
	Graft loss	Inconclusive (RR: 0.26; 95% CI: 0.03–2.20; p=0.21)	1 RCT[112] N=83	Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.34; 95% CI: 0.01–8.14; p=0.51)	1 RCT[112] N=83	Imprecision	Insufficient
	CMV infection	Inconclusive (RR: 1.23; 95% CI: 0.41–3.72; p=0.71)	1 RCT[112] N=83	Imprecision	Insufficient
	Other opportunistic Infections	Associated with higher incidence of other infections (RR: 2.22; 95% CI: 0.93–5.28; p=0.07)	1 RCT[112] N=83	Imprecision	Low
mTOR inhibitors vs. Tacrolimus, with alemtuzumab induction in both groups	Renal function	SRL associated with improved renal function (1.83±0.88 mL/second vs. 1.38±0.48 mL/second, p<0.05)	1 RCT[113] N=21	Study Limitations Imprecision	Low
	BPAR	Inconclusive (RR: 0.44; 95% CI: 0.11–1.78; p=0.25)	1 RCT[113] N=21	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 2.20; 95% CI: 0.23–20.72; p=0.49)	1 RCT[113] N=21	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.36; 95% CI: 0.02–8.03; p=0.52)	1 RCT[113] N=21	Study Limitations Imprecision	Insufficient
	BPAR	Inconclusive (RR: 0.44; 95% CI: 0.11–1.78; p=0.25)	1 RCT[113] N=21	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 2.20; 95% CI: 0.23–20.72; p=0.49)	1 RCT[113] N=21	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 0.36; 95% CI: 0.02–8.03; p=0.52)	1 RCT[113] N=21	Study Limitations Imprecision	Insufficient

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations; Precision; Consistency; Directness; Reporting Bias.
AZA=Azathioprine; BPAR=Biopsy proven acute rejection; CI=Confidence interval; CMV=Cytomegalovirus; CNI=Calcineurin inhibitor; CsA=Cyclosporine; eGFR=Estimated glomerular filtration rate; MMF=Mycophenolate mofetil; mTOR=Mammalian target of rapamycin; NS=Not significant; rATG=rabbit anti-thymocyte globulin; RCT=Randomized controlled trial; RR=Relative risk; SMD=Standardized mean difference; SRL = Sirolimus; TAC = Tacrolimus

Head-to-Head Studies

Description of Head-to-Head Studies

Eight studies directly compared a CNI minimization regimen to CNI conversion, withdrawal, or avoidance strategies (Table 21). These studies did not have a standard-dose CNI arm to serve as a conventional control group. Five studies compared minimization to conversion: two converted patients from low-dose CsA to SRL,[114,115] one converted patients from low-dose TAC to SRL,[116] and two converted subjects from low-dose CNI (CsA or TAC) to EVR[117] or unspecified "rapamycin."[118] In addition to the studies comparing minimization to conversion, one study compared low-dose TAC to withdrawal of TAC.[119] Finally, two studies compared low-dose TAC to avoidance strategies based on SRL.[120,121]

These studies differed from the previous sets of trials in population as well as design. Head-to-head studies were generally smaller than the other studies reviewed. Six of the eight studies (75%) enrolled fewer than 100 patients, while just 27 of the 76 studies (36%) addressing other regimens had populations of fewer than 100. The head-to-head studies also included populations at higher risk for poor outcomes. Four of the eight head-to-head trials included only patients with chronic allograft nephropathy, while only four of the other 76 studies we reviewed (three minimization studies and one withdrawal study) were limited to that population. Another of the head-to-head trials[121] focused more generally on higher-risk participants, including a large proportion of African-American patients (71%), older patients (30% were older than 50 years old), and a large proportion of patients with delayed graft function (47%).

Seven studies were evaluated as high risk of bias, due to poor adherence to study regimens, low rates of study completion, industry funding, and failure to report important characteristics of study randomization and enrollment.

Table 21. Head-to-head studies

Reference	Minimization	Other Intervention	N, Intervention	N, Control
Stallone 2005[118]	CNI, MMF	Conversion to SRL	50	34
Han 2011[114]	CsA, MMF	Conversion to SRL, MMF	29	22
Liu 2007[115]	CsA, MMF	Conversion to SRL, MMF	54	56
Pankewycz 2011[116]	TAC, MPS	Conversion to SRL, MMF	29	23
Cataneo-Davila 2009[117]	CNI, EVR	Conversion to EVR	10	10
Burkhalter 2012[119]	TAC, SRL, MPS	Withdrawal of TAC	19	18
Hamdy 2005[120]	TAC, SRL	Avoidance with SRL, MMF	65	65
Lo 2004[121]	TAC	Avoidance with SRL	41	29

CNI=Calcineurin inhibitor; CsA=Cyclosporine; MMF=Mycophenolate mofetil; MPS=Mycophenolate sodium; SRL=Sirolimus; TAC=Tacrolimus

Key Points

- Head-to-head studies were smaller and included more high-risk patients than other types of studies evaluated in this report.
- Two studies that compared a regimen of low-dose TAC and SRL to CNI avoidance using SRL and MMF, found that the avoidance strategy was associated with better renal function (Strength of Evidence: Low.) Results were inconclusive for other outcomes.

- One study that compared a regimen using low-dose CsA and MMF to a regimen that used conversion to an mTOR inhibitor, found that the conversion regimen was associated with improved renal function (Strength of Evidence: Moderate) and reduced risk of graft loss (Strength of Evidence: Low.)
- Additional direct comparative studies are needed to inform the evidence base.

Detailed Synthesis of Head-to-Head Studies

Two studies that compared low-dose CsA with conversion from CsA to an mTOR inhibitor provided low-strength evidence suggesting that conversion was associated with improved renal function and lower risk of graft loss.[115,118] These two studies were inconclusive for the outcome of acute rejection. The other three conversion studies did not provide sufficient evidence to draw conclusions for any of the outcomes we assessed.[117-119]

Two studies comparing low-dose TAC to CNI avoidance with SRL found low strength evidence that treatment with an mTOR inhibitor was associated with improved eGFR.[120,121] Results were inconclusive for all other outcomes. Finally, Burkhalter et al.[119] compared a regimen of low-dose TAC, SRL, and MPS to a regimen that maintained SRL and MPS while withdrawing TAC. The study did not provide conclusive findings at 6 months. After 1 year, SRL had been discontinued for most of the patients in both study groups due to adverse events.

Applicability

As noted above, these studies were more likely than others in this report to include patients at higher risk for adverse outcomes. These studies are therefore potentially more relevant to important population subgroups. However, adherence to study groups and study completion rates was low in several studies, which may limit the generalizability of the results.

Summary

We identified only 8 RCTs that conducted head-to-head comparisons of CNI minimization with other alternative immunosuppressive regimens. Four studies reported improved renal function in patients who did not receive or were converted from CNI, and 2 studies found conversion was associated with lower risk of graft loss. This evidence base was not sufficient to support conclusions for the other comparisons and outcomes examined. Additional head-to-head studies are needed to further build the evidence base for the comparative effectiveness of CNI minimization versus other alternative immunosuppressive strategies.

Table 22. Strength-of-evidence table for head-to-head studies

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Reduced CNI + mycophenolate mofetil vs. Conversion from CNI to mTOR inhibitor	Renal function	Inconclusive (47 mL/min vs. 53 mL/min; p=0.22)	1 RCT[118] N=84	Imprecision	Insufficient
	BPAR	Inconclusive; no events observed	1 RCT[118] N=84	Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 5.44; 95% CI: 0.71–41.53; p=0.10)	1 RCT[118] N=84	Imprecision	Insufficient
	Patient death	Inconclusive; no events observed	1 RCT[118] N=84	Imprecision	Insufficient
Reduced cyclosporine + mycophenolate mofetil vs. Conversion from cyclosporine to mTOR inhibitor	Renal function	Conversion associated with improved renal function (one study reported higher eGFR in conversion group, p<0.05, data not available;[115] one study reported eGFR: 37 mL/min for minimization vs. 50 mL/min for conversion; p<0.05;[116])	2 RCT[114,115] N=161	Study Limitations	Moderate
	BPAR	Inconclusive (RR: 0.76; 95% CI: 0.12–4.97; p=0.77)	1 RCT[115] N=51	Study Limitations Imprecision	Insufficient
	Graft loss	Conversion associated with reduced risk of graft loss (one study reported "graft survival estimate" favoring conversion: 55% vs. 77%;[115] one study reported "graft survival ratio was markedly higher in conversion group"[116])	2 RCT[114,115] N=161	Study Limitations Imprecision	Low
Reduced tacrolimus + mycophenolate mofetil vs. Conversion from tacrolimus to mTOR inhibitor, with rATG induction	Renal function	Inconclusive (74 mL/min vs. 66 mL/min; p=0.09)	1 RCT[116] N=52	Study Limitations Imprecision	Insufficient
	BPAR	Inconclusive (RR: 0.27; 95% CI: 0.01–6.26; p=0.41)	1 RCT[116] N=52	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 0.27; 95% CI: 0.01–6.26; p=0.41)	1 RCT[116] N=52	Study Limitations Imprecision	Insufficient
	BK infection	Inconclusive (RR: 2.40; 95% CI: 0.10–56.30; p=0.59)	1 RCT[116] N=52	Study Limitations Imprecision	Insufficient
Reduced CNI + mTOR inhibitors vs. Conversion from CNI to mTOR inhibitors + either mycophenolate mofetil or azathioprine	Renal function	Inconclusive (76 mL/min vs. 66 mL/min; p=0.26)	1 RCT[117] N=20	Study Limitations Imprecision	Insufficient
	BPAR	Inconclusive (RR: 3.00; 95% CI: 0.14–65.90; p=0.49)	1 RCT[117] N=20	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive; no events observed	1 RCT[117] N=20	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive; no events observed	1 RCT[117] N=20	Study Limitations Imprecision	Insufficient

Table 22. Strength-of-evidence table for head-to-head studies (continued)

Comparison	Outcome	Conclusion	Quantity and Type of Evidence	Factors That Weaken the Strength of Evidence*	Overall Evidence Strength
Reduced tacrolimus + mTOR inhibitors + mycophenolic sodium vs. Withdrawal of tacrolimus + mTOR inhibitors + mycophenolic sodium	Renal function	Inconclusive (52 mL/min vs. 45 mL/min; p=0.25)	1 RCT[119] N=37	Study Limitations Imprecision	Insufficient
	BPAR	Inconclusive (RR: 0.47; 95% CI: 0.05–4.78; p=0.53)	1 RCT[119] N=37	Study Limitations Imprecision	Insufficient
Reduced tacrolimus + mTOR inhibitors + basiliximab induction vs. mTOR inhibitors + mycophenolate mofetil + basiliximab induction	Renal function	Minimization associated with lower eGFR compared to avoidance (79.6 mL/min vs. 94.9 mL/min; p<0.05)	1 RCT[120] N=130	Study Limitations Imprecision	Low
	BPAR	Inconclusive (RR: 1.33; 95% CI: 0.60–2.95; p=0.48)	1 RCT[120] N=130	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 1.33; 95% CI: 0.31–5.72; p=0.70)	1 RCT[120] N=130	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 5.00; 95% CI: 0.24–102.16; p=0.30)	1 RCT[120] N=130	Study Limitations Imprecision	Insufficient
	Other opportunistic Infections	Inconclusive (RR: 0.09; 95% CI: 0.01–1.61; p=0.10)	1 RCT[120] N=130	Study Limitations Imprecision	Insufficient
Reduced tacrolimus + mTOR inhibitors + rATG induction vs. mTOR inhibitors + mycophenolate mofetil + rATG induction	Renal function	Minimization associated with lower eGFR compared to avoidance (52.9 mL/min vs. 72.4 mL/min; p<0.05)	1 RCT[121] N=70	Study Limitations Imprecision	Low
	BPAR	Inconclusive (RR: 1.41; 95% CI: 0.28–7.22; p=0.68)	1 RCT[121] N=70	Study Limitations Imprecision	Insufficient
	Graft loss	Inconclusive (RR: 1.89; 95% CI: 0.55–6.51; p=0.32)	1 RCT[121] N=70	Study Limitations Imprecision	Insufficient
	Patient death	Inconclusive (RR: 2.14; 95% CI: 0.09–50.82; p=0.64)	1 RCT[121] N=70	Study Limitations Imprecision	Insufficient

*The following factors were assessed for potential effect on the strength of evidence: Study Limitations; Precision; Consistency; Directness; Reporting Bias.
BPAR=Biopsy proven acute rejection; CI=Confidence interval; CMV=Cytomegalovirus; CNI=Calcineurin inhibitor; eGFR=Estimated glomerular filtration rate; mTOR=Mammalian target of rapamycin; rATG=rabbit anti-thymocyte globulin; RCT=Randomized controlled trial; RR=Relative risk; SMD=Standardized mean difference

Discussion

Below, we summarize the main findings and their strength of evidence. We then discuss the findings in relation to what is already known, applicability of the findings, implications for decisionmaking, limitations, research gaps, and conclusions. When we have graded evidence as insufficient, it indicates that evidence is either unavailable, does not permit estimation of an effect, or does not permit us to draw a conclusion with at least a low level of confidence. It does not indicate that a treatment has been proven to lack efficacy.

Key Findings and Strength of Evidence

Key Question 1

One small study with high risk of bias reported on clinical validity outcomes. The evidence from this study was considered insufficient to permit conclusions about the comparative performance of HPLC versus immunoassay for clinical outcomes. The findings of seven studies assessing analytical performance suggest that chromatographic methods are more accurate and precise than commonly used immunoassays at measuring TAC drug levels. However, it is unclear if the differences identified in these studies are clinically meaningful such that they would change clinical management or affect patient outcomes.

Key Question 2

The findings of the studies that made up the evidence base for this question showed low strength of evidence suggesting that risk of biopsy proven acute rejection (BPAR) is similar between new renal transplants monitored at trough level (C0) and those monitored at two hours (C2). For the most part, the evidence for patient and graft loss and adverse events among studies comparing C0 to C2 monitoring in new renal transplants was inconclusive due to study limitationsand imprecision of findings.

However, low strength of evidence from one randomized controlled trial (RCT) indicated that C2 monitoring led to a significantly higher Cyclosporine A (CsA) mean cumulative dose increase compared to C0 monitoring. Low strength of evidence from this same study also indicated that significantly more patients in the C2 group than in the C0 group experienced tremors. In contrast, low strength of evidence from one small RCT indicated that C2 monitoring led to significantly more CsA dose reductions than C0 monitoring among stable renal recipients.

The discrepancy of the findings related to CsA dose may be due to the difference in time post-transplant of patients in the studies. In one study, the patients were new transplants, and were only 20 days post-transplant, whereas in the other study they were stable transplants, with 3 or more months since transplant. CsA levels tend to be more variable shortly after transplantation, and reaching target levels is often difficult. In addition, the C2 target levels in the study examining newer transplants were somewhat higher than in the other studies that address this question. Target C2 levels in the other studies ranged from 1,100 to 1,400 µg/L compared to 1,500 to 2,000 µg/L in the study of newer transplants. Alternatively, the explanation may be the single-study evidence base for each conclusion; future studies could overturn these conclusions.

Key Questions 3A and 3B

Four types of immunosuppressive regimens designed to reduce calcineurin inhibitor (CNI) exposure were assessed. High- and moderate-strength evidence suggests that minimization strategies based on lower doses of CsA or TAC result in significantly better clinical outcomes compared with standard-dose regimens and provide a superior combination of increased benefits and reduced harms than approaches using conversion, withdrawal, or avoidance. Low-dose therapy was associated with reduced risk for acute rejection, graft loss, and opportunistic infections. Minimization was also associated with improved renal function as measured by estimated glomerular filtration rate (eGFR.) These benefits were associated with both CsA and TAC, and with adjunctive use of either mycophenolic acid–based therapy such as mycophenolate mofetil (MMF) or mycophenolic sodium (MPS), or mammalian target of rapamycin (mTOR) inhibitors, including sirolimus (SRL) and everolimus (EVR.) High-strength evidence also indicates that minimization may be most effective when initiated immediately or shortly following transplant and may be less effective when implemented 6 or more months after transplant.

The evidence base addressing induction therapy used in conjunction with CNI minimization is inconclusive and needs further research, although studies suggest that use of induction therapy may not be necessary to achieve the improved outcomes associated with CNI minimization. We were unable to evaluate the role of induction therapy for conversion, withdrawal, or avoidance strategies because sub-groups were too small for analysis due to heterogeneity of regimens and non-reporting of induction agent use. Additionally, induction therapy likely has limited clinical relevance to many of these studies because conversion and withdrawal strategies were usually initiated at least several months post-transplant, when the impact of induction treatment would be minimized.

Similarly, moderate-strength evidence indicated that conversion to an mTOR inhibitor or belatacept was associated with modest improvement in renal function compared to standard-dose CNI regimens. High-strength evidence also suggested that conversion to an mTOR inhibitor was associated with a decreased risk in the incidence of cytomegalovirus (CMV) infection. However, high- and moderate-strength evidence suggested that conversion from a CNI regimen to an mTOR inhibitor, MPS, or belatacept was associated with an increased risk of BPAR. For all other outcomes—patient or graft loss and other infection-related adverse events—moderate-strength evidence suggests no difference converting to another immunosuppressant agent or remaining on a CNI-based regimen. More controlled trials with longer followup may be needed to better understand the impact of conversion on longer term outcomes, such as patient and graft loss, and among higher risk for these outcomes.

High- and moderate-strength evidence suggests that planned withdrawal of CNI may result in improved renal function but is also associated with increased risk of acute rejection. Risk for acute rejection was higher in studies that used either mycophenolic acid–based treatment or mTOR inhibitors. The evidence base was insufficient to support conclusions for most of the outcomes examined.

Avoidance strategies were examined in only eight studies, each of which used either SRL or belatacept as the primary alternative to CNI therapy. The evidence base for most outcomes was considered insufficient, and further research on de novo avoidance of CNI treatment is necessary.

All these studies compared standard-dose CNI regimens with strategies designed to reduce CNI toxicity. Our review also identified eight trials that examined head-to-head comparisons

between low-dose CNI and approaches that used conversion, withdrawal, or avoidance. Some of these studies suggest a beneficial effect on renal function associated with conversion or avoidance. However, the studies are heterogeneous and enrolled small numbers of patients, and the overall evidence base is insufficient to draw conclusions.

Findings in Relation to What Is Already Known

Several systematic reviews have examined different aspects of CNI management in renal transplant patients. One previous review examined studies comparing the clinical outcomes of patients on CsA-based therapy monitored with C2 levels to those monitored by C0 levels. Knight and Morris evaluated the evidence from trials evaluating the impact of C2 versus C0 monitoring on clinical outcomes among renal, liver, and cardiac transplant recipients.[10] The evidence base for renal transplant recipients consisted of 13 studies, most of which were single- group pre-post studies. These studies were not included in this review. However, despite differences in the evidence base, the conclusions drawn in the Knight and Morris review were similar to this review. These authors found evidence that C2 monitoring was associated with detecting higher levels of CNI than C0, but no clear evidence that C2 monitoring affects renal function or acute rejection. Thus, Knight and Morris concluded that little evidence from prospective studies supports the theoretical benefits of C2 monitoring.

The other previous reviews focused on evaluating the benefits and harms associated with changing from a standard CNI regimen to an alternative regimen, specifically minimization and withdrawal,[12,122] avoidance and withdrawal,[123] and conversion to an mTOR inhibitor.[124]

Su et al.[122] recently completed a systematic review of seven RCTs that examined CNI minimization or withdrawal with use of the mTOR inhibitor EVR. The alternative strategies used in these studies were associated with increased eGFR, lower serum creatinine, and no difference in graft loss or death. Low-dose regimens were associated with no difference in BPAR, while rejection risk was higher in studies that avoided CNI. Additionally, patients on EVR had lower risk of CMV infection but were at greater risk for nonfatal adverse events. Moore et al.[12] reviewed 19 RCTs that evaluated CNI minimization or withdrawal with use of MMF or MPS. Minimization regimens were associated with improved renal function, as measured by GFR, and reduced risk of graft loss. No harms were increased in the minimization trials. Conversely, withdrawal studies were associated with greater risk of BPAR and improved GFR and serum creatinine. These results are consistent with our meta-analyses, which found significant benefits associated with low-dose approaches to CNI management, but lesser benefits and potential harms resulting from CNI withdrawal regimens.

Yan's recent review[124] identified 11 RCTs of withdrawal strategies and 16 RCTs that used CNI avoidance. Early withdrawal and SRL-based avoidance were associated with improved renal function and no difference in graft loss, patient survival, or adverse events. These regimens also resulted in higher risk of BPAR at 1 year, but no significant differences were observed at 2 years after transplant.

Lim and colleagues conducted a recent systematic review of RCTs comparing delayed conversion from CNIs to mTOR inhibitors versus remaining on CNIs.[124] The overall evidence base for this review consisted of 27 trials; however, only 13 trials reported on outcomes of interest to the review and contributed to primary analyses conducted in the review. Most of these trials were included in the present review. The primary outcomes analyzed in the Lim review included renal function (as measured by GFR), acute rejection, mortality, graft loss, and adverse events. Similar to the results in this review, Lim et al. found that patients converted to an mTOR

inhibitor had slightly higher GFR at 1-year followup than patients remaining on a CNI. The results of their GFR analysis also indicated the presence of substantial heterogeneity (I^2=68%) that was not explained by time post-transplant or type of mTOR inhibitor. Lim et al.'s findings also indicated that rejection risk was higher among patients converted to an mTOR inhibitor. Finally, like this review, Lim et al. found that conversion to an mTOR inhibitor was associated with fewer reported incidences of CMV. However, they indicated that discontinuation secondary to adverse events was generally higher among patients converting to an mTOR inhibitor.

Applicability

Four important factors limit the applicability of these findings to patient care. First, populations at higher risk for graft rejection, infection, or other poor outcomes are not well-represented in the evidence base. Many of the RCTs included in this review excluded highly sensitized populations, retransplants, and patients with significant comorbid conditions. These trials did not report socioeconomic status, and 19 studies excluded patients over age 65. No studies focused exclusively on graft recipients with demographic characteristics often associated with greater risk for acute rejection, such as African-Americans, and almost no studies stratified results by this factor or by age or immunologic risk. Additionally, we excluded studies in multi-organ transplant populations. Therefore, this evidence base may not indicate how changes in standard CNI regimens might affect important subpopulations of renal transplant recipients.

Second, these RCTs implemented alternative CNI regimens as planned strategies in patients randomly assigned to treatment or control groups. Transplant recipients who required a regimen change due to CNI toxicity were not specifically studied in these trials, nor were these patients analyzed separately. Thus, the evidence base may not reflect how minimization, conversion, or withdrawal strategies affect outcomes in patients who have experienced CNI-related adverse events.

Third, minimization regimens varied widely in selection of low-dose target levels. Standard definitions for low-dose targets do not exist, and the evidence base does not indicate optimal levels for reducing CsA or TAC exposure. Similarly, achievement of low-dose CNI target levels for minimization regimens was poorly and inconsistently reported and varied across studies.

Finally, it is important to note that we examined only immunosuppression for renal transplant recipients. The results of these studies may not apply to CNI therapy for patients with liver, pancreas, other solid organ transplants, or to patients who receive sequential or combination organ transplants.

Implications for Clinical and Policy Decisionmaking

The evidence base examined in this systematic review has important implications for clinicians involved in the care of renal transplant recipients, most notably transplant surgeons, nephrologists, pharmacists, nurses, and infectious disease specialists. To reduce the risk of CNI-associated toxicity and adverse events, treatment with low-dose CsA or TAC in combination with MMF, MPS, or mTOR inhibitors may provide sufficient immunosuppressive therapy to reduce risk of acute rejection and opportunistic infection, while enabling improved renal function. Conversion or withdrawal strategies may also help improve renal function but can result in higher risk for acute rejection. The potential benefits and risks of de novo CNI avoidance are unclear.

Clinicians must carefully weigh many therapeutic options when evaluating which immunosuppressive regimen to implement and must consider each patient's immunologic risk

and comorbid medical conditions. The studies assessed in this review were conducted primarily in low-risk populations and may therefore be less applicable to higher-risk patients. Clinicians must also consider patient adherence to medication regimens, potential interactions between immunosuppressive drugs and other medications, and the risk of discontinuation resulting from drug side effects.

Medication costs are an important consideration for patients, clinicians, health insurers, and policymakers. While Medicare often provides 80% of coverage of immunosuppression for up to 3 years following renal transplantation, the burden of paying for immunosuppression in the longer term may fall disproportionately on patients and their families if Medicare entitlement was based solely on end-stage renal disease. CsA, TAC, MMF, MPS, and mTOR inhibitors are available in generic formulations, but belatacept is not.

Another important consideration is the growing body of research on pharmacogenetic testing. Development of validated biomarkers may help clinicians better individualize immunosuppressive regimens and potentially prolong patient and graft survival by minimizing long-term drug toxicity.

Monitoring therapeutic drug levels is a critical component of CNI management. Although the evidence base for KQ 1 is limited, the ease of use of immunoassays may outweigh any potential improvements in analytic validity resulting from the use of HPLC methodologies. Similarly, preferences for CO or C2 monitoring of CsA may be influenced as much by practical considerations (such as patient convenience) as the evidence base for KQ 2.

Limitations of the Comparative-Effectiveness Review Process

Due to the broad scope of the Key Questions, the many potentially relevant studies, and the time and resources available to complete the review, we confined our final analyses to RCTs for KQ 3. Many observational studies have been published that address this topic, and by excluding non-RCTs we theoretically could have omitted important findings, especially findings related to adverse events. However, our systematic searches did not exclude observational studies, thus we reviewed their characteristics, and found that they were generally small in size, did not have extended followup periods, and their reported outcomes were represented adequately by the available RCTs.

We also limited our review to studies published in English, which could have led to exclusion of important articles published in other languages. However, we included 21 studies representing 1,848 subjects from countries outside of North America, Western Europe, and Australia, including studies conducted in Asia, the Middle East, and South America.

Another limitation of the systematic review and meta-analytic process is that combining multiple studies into broad analytic categories can mask important sources of heterogeneity. For example, studies that used an mTOR inhibitor were frequently combined, whether they used SRL or EVR, because their pharmacologic mechanisms are similar. Studies also varied in whether and how they excluded higher-risk patients, in how they measured renal function, and in the selection of medication dosing and therapeutic targets. We performed numerous subgroup analyses to address important types of study variation and conducted sensitivity analyses to explore heterogeneity. However, we could not explore every potentially important source of variance given the complexity of immunosuppression management in transplant recipients.

Limitations of the Evidence Base

Very few studies addressed KQs 1 and 2. They were highly complex and heterogeneous, and we were not able to conduct meta-analysis given these limitations. Only one RCT examined clinical outcomes of different monitoring methods. Most of the studies were not randomized and used pre-post study designs.

We identified more than 80 RCTs that addressed KQ 3, which is a robust evidence base. However, variations in patient populations and medication regimens may limit the generalizability of individual studies as well as our meta-analyses.

Small sample size was an important limitation in many studies as well. Although we were able to perform meta-analyses of many key outcomes, small studies can yield imprecise statistical estimates. Sample size was an important limitation in our evaluation of low-frequency events, such as patient death, graft loss, and BK virus infection. Similarly, incomplete and inconsistent reporting of adverse events limited our ability to adequately assess the potential impact of alternative CNI strategies on patient harms. This was particularly important for CNI-related nephrotoxicity and chronic allograft dysfunction, which were not assessed systematically in this review because too few studies reported comparable data for these outcomes.

Another major limitation is the short followup period reported in most studies. We used 1-year outcome data whenever possible in our review because that was the time period reported most consistently. Longer-term outcomes are important to patients and clinicians, though, and may provide better insight into the effect of CNI management strategies. However, very few studies examined long-term results.

Patient adherence to prescribed CNI regimens is another important factor that limits our findings. Measures of adherence were not consistently reported, and failure of patients to remain on CNI regimens may account for poorer outcomes or limited clinical improvement. Similarly, imperfect fidelity to monitoring protocols (e.g., variation in when clinical staff actually collect samples for laboratory testing) was an inherent limitation of many RCTs. Another limitation is the potential imprecision in laboratory results, between and within labs, which may affect the validity of individual study results.

Finally, we should emphasize that most of the studies we reviewed were conducted in low- or average-risk populations and were implemented as planned strategies rather than therapeutic responses to patients who exhibited CNI-related adverse events.

Research Gaps

For KQs 1 and 2, more studies are needed that directly compare analytical and clinical outcomes between different monitoring techniques. Studies comparing different monitoring methods also need to consider the associated resources and costs with different methods, patient and clinician preferences, and availability of specific methods, such as HPLC. In addition, they need to include longer followup periods. Comparisons of monitoring techniques are particularly important because long-term overexposure to immunosuppression could potentially contribute to post-transplant complications such as infection, malignancy, cardiovascular disease, diabetes, and related allograft changes (formerly known as chronic allograft nephropathy).

Although our review identified a large number of studies examining KQ 3, significant knowledge gaps require additional research. Studies in high-risk populations are necessary to provide evidence for how to manage immunosuppression in elderly renal transplant patients, African-Americans, those of lower socioeconomic status, patients who have undergone

retransplantation, and those living with significant comorbidities, including human immunodeficiency virus (HIV).

More studies are necessary to understand the role of induction agents, particularly in low-dose CNI regimens and avoidance strategies. While many studies have examined induction therapy independently, data on their effectiveness within these alternative regimens are missing.

We identified few head-to-head comparisons of alternative regimens, but these types of studies will be essential for informing real-world clinical practice. Data from direct comparative-effectiveness trials will help clinicians understand the benefits and risks of alternative immunosuppression regimens. Studies are also necessary to better understand the role of belatacept therapy, which was included in very few RCTs.

Studies must seek to measure and report patient-centered outcomes, including preferences for different medications, adherence to immunosuppressive therapy, and side effects of CNIs and other immunosuppressants. Finally, data from longer-term followup are lacking. Studies assessing effectiveness, harm, and patient adherence at 5, 10, and 15 years after implementation of alternative regimens would be invaluable for clinicians and patients.

Conclusions

The findings of the studies addressing analytic validity suggest that chromatographic techniques (e.g., HPLC, LC-MS/MS) more accurately measure CNI concentration levels than commonly used immunoassays. However, it is unclear if the differences identified in these studies are clinically meaningful such that they would change clinical management or affect patient outcomes. In addition, these techniques are typically more expensive, time-consuming, labor-intensive, and less standardized, and thus their results may be more provider-dependent.

For KQ 2, the current state of the evidence does not suggest any clear clinical benefit of C2 monitoring over C0; however, low strength of evidence suggests that risk of biopsy proven acute rejection (BPAR) is similar between new renal transplants monitored at trough level (C0) and those monitored at two hours (C2). One randomized controlled trial (RCT) indicated that C2 monitoring led to a significantly higher Cyclosporine A (CsA) mean cumulative dose increase compared to C0 monitoring in recent transplant recipients. Low strength of evidence from this same study also indicated that significantly more patients in the C2 group than in the C0 group experienced tremors. In contrast, another small RCT indicated that C2 monitoring led to significantly more CsA dose reductions than C0 monitoring among stable renal recipients. Whether this reflects actual differences between recent and stable renal recipients, or simply reflects the fact that each is based on a single study, is uncertain. It is possible that future studies could overturn these conclusions.

For KQ 3, many studies suggest that immunosuppression with low-dose CsA or TAC, in combination with mycophenolic acid formulations or mTOR inhibitors, results in improved renal function and reduced risk of harm. The beneficial effects of minimization strategies may be most significant when initiated from the time of transplant or shortly thereafter. Use of induction agents is not strongly associated with improved outcomes in minimization regimens, but additional research is necessary to clarify the effect of induction therapy. Conversion from a CNI to an mTOR inhibitor is associated with modest improvement in renal function but also with higher incidence of acute rejection. Conversion was associated with a slightly lower risk of CMV, but the evidence was inconclusive for other opportunistic infections. Withdrawal of a CNI was not associated with improvements in renal function and may increase the risk of acute rejection. Avoidance strategies employing de novo use of SRL, EVR, or belatacept have not

been studied widely, and further research is necessary to identify potential benefits or harms of CNI avoidance.

These regimens have been studied primarily in low-risk populations, and further research is necessary to identify successful immunosuppression strategies for high-risk patients. More comprehensive and consistent reporting of important outcomes is needed, including measures of renal function, CNI-related toxicity, and patient adherence to immunosuppressive regimens.

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Abbreviations and Acronyms

AR–Acute rejection
ABS–Affect balance scale
AUC–Areas under curve
AZA–Azathioprine
ATG/rATG–Anti-thymocyte globulin
BEL–Belatacept
BPAR–Biopsy proven acute rejection
BP–Blood Pressure
BK–Polyomavirus
CMV–Cytomegalovirus
CNI–Calcineurin Inhibitors
CsA–Cyclosporine A
CES-D–Center of epidemiological studies depression scale
CrCl–Creatinine Clearance
CAN–Chronic Allograft Nephropathy
DGF–Delayed Graft Function
EVR–Everolimus
FPIA/FPLA–Fluorescence polarization immunoassay
eGFR–Estimated glomerular filtration rate
GI–Gastrointestinal
GGT–Gamma glutamyltransferase
HBV–Hepatitis B
HDL–High Density Lipoprotein
HIV–Human Immunodeficiency Virus
HPLC–High performance liquid chromatography
IFTA–Interstitial fibrosis and tubular atrophy on kidney allograft biopsy
IA–Immunoassay
LC–Liquid Chromatography
LDL–Low Density Lipoprotein
MMF–Mycophenolate mofetil group
MPS–Mycophenolate Sodium
MS–Mass Spectrometry
MPA–Medroxyprogesterone acetate
NR–Not Reported
NA–Not Applicable
PRED–Prednisone
PRA–Panel Reactive Antibody
PCP–Pneumocystis carinii pneumonia
SIP–Sickness impact profile
SRL–Sirolimus
STER–Steroid
TAC–Tacrolimus
TACex–patients receiving TAC without criteria to undergo intervention at month 3
UTI–Urinary tract infection